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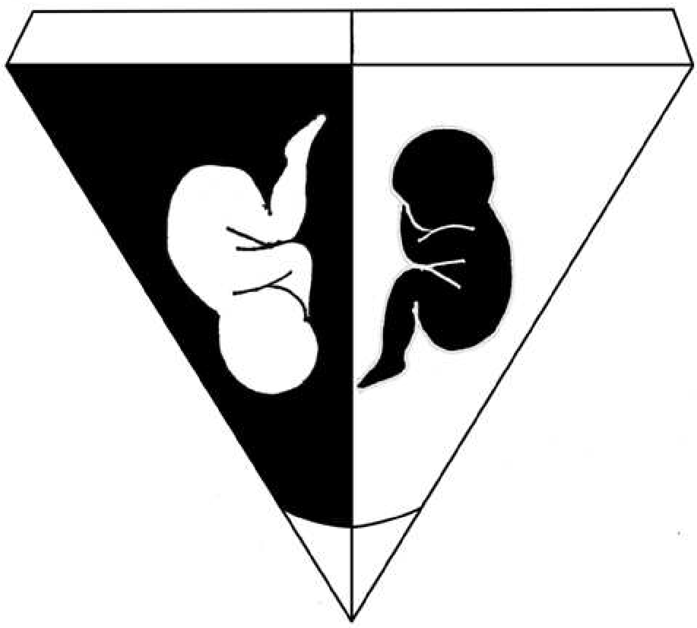
TIMING AND MODE OF DELIVERY IN TWINS:

The ongoing controversy



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Doutoramento em Medicina

Especialidade em Ginecologia e Obstetrícia

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To my parents

To my sons Frederico and Guilherme

To all parents of twins

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Acknowledgements

The work presented here would not have been possible without the help of patients, friends and colleagues.

In particular, I would first like to thank my thesis advisor, Professor Luís Graça, for his continuous support and assistance in producing this work.

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List of Abbreviations

AC	Abdominal circumference
ACOG	American College of Obstetricians and Gynecologists
ART	Assisted reproductive technology
BMI	Body Mass Index
CI	Confidence interval
CL	Cervical length
CNGOF	Collège National des Gynécologues et Obstétriciens Français
CRL	Crown-rump length
CS	Cesarean section
DC	Dichorionic-twins
DZ	Dizygotic twins
EFW	Estimated fetal weight
€	Euro
GDM	Gestational diabetes
ICSI	Intracytoplasmatic sperm injection
IO	Intra-uterine insemination
INE	Instituto Nacional de Estatística
IVH	Intraventricular hemorrhage
IVF	In Vitro Fertilization
IUFD	Intra-uterine fetal death
IUGR	Intrauterine growth restriction
LBW	Low birth weight
MAC	Maternidade Dr. Alfredo da Costa
MC-DA	Monochorionic-diamniotic twins
MC-MA	Monochorionic-monoamniotic twins
MZ	Monozygotic twins
NICE	National Institute for Health and Clinical Excellence
NICU	Neonatal intensive care Unit
NRM	Neonatal respiratory morbidity
OI	Ovulation Induction
OR	Odds ratio
PE	Preeclampsia
PPROM	Preterm premature rupture of membranes
PROM	Premature rupture of membranes
PUPPP	Pruritic urticarial papules and plaques of pregnancy
RDS	Respiratory distress syndrome
RCOG	Royal College of Obstetricians and Gynaecologists
RANZCOG	Royal Australian and New Zealand C. of Obstetricians and Gynaecologists
SB	Stillbirth
SGA	Small for gestational age
SO	Superovulation
SOGC	Society of Obstetricians and Gynaecologists of Canada
TAPS	Anemia-polycythemia sequence
TTN	Transient tachypnea of the newborn
TTTS	Twin-twin transfusion syndrome
WKS	Weeks
USA	United States of America
VS	Versus

Resumo

Chamam-se gémeos às crianças nascidas de uma mesma gravidez. Podem resultar de um zigoto - Monozigóticos (MZ), ou de vários zigotos - Dizigóticos (DZ). Os gémeos DZ possuem tantas placentas e bolsas amnióticas como fetos - Dicoriónicos (DC). Os gémeos MZ são também DC em 18 a 30% dos casos e nos restantes têm uma só placenta para todos os fetos – Monocoriónicos (MC). Neste último tipo de gémeos, em 60-70% dos casos cada feto tem a sua bolsa amniótica – gémeos MC diamnióticos (DA) e em 1 a 2% dos casos existe apenas uma única bolsa – gémeos MC monoamnióticos (MA).

Os partos gemelares representam na atualidade 30‰ de todos os partos em Portugal. A gravidez múltipla é uma gravidez de alto risco e o seu sucesso obstétrico depende do diagnóstico atempado das diversas complicações maternas e fetais.

Nesta tese tentámos estabelecer um método ecográfico eficaz para identificar a existência de discordância de peso entre os gémeos superior a 25%. Analisar o efeito das variações no Índice de massa corporal nas grávidas de gémeos e avaliar os fatores de risco e o impacto da diabetes gestacional.

Contudo o principal objetivo desta tese foi determinar a idade gestacional adequada para o parto nas gravidezes múltiplas sem complicações, a segurança da indução do trabalho de parto e a morbilidade materna do parto por cesariana (CS).

A nossa experiência e as recomendações atuais sugerem efetuar o parto nos gémeos DC com 37-38 semanas, nos MC-DA com 36-37 e nos MC-MA com 32-34 semanas.

O parto vaginal induzido com protocolo idêntico ao da gravidez simples pode ser considerado nos gémeos DC e MC-DA, cefálico-cefálico e cefálico-não cefálico. O misoprostol é uma droga segura na indução de trabalho de parto em gémeos. A CS é recomendada para os MC-MA, quando o 1º gémeo não é cefálico, quando o 2º gémeo é ≥40% maior que o 1º e no útero com cirurgia prévia. Temos sempre o dever de informar os casais sobre o risco do parto vaginal e da CS e a via de parto deve ter em linha de conta a experiência em manobras obstétricas da equipa que o vai realizar.

Summary

Twins occur when more than one offspring is produced in the same pregnancy. They can result from one or several zygotes – Monozygotic (MZ) and Dizygotic (DZ) twins. DZ twins are always dichorionics (DC) with as many placentas and amniotic sacs as the number of fetuses. MZ twins can also be dichorionic (18-30%) or have only one placenta – monochorionic (MC). This last kind of twins might have one amniotic sac for each fetus (60-70%) – MC-DA twins, or only one amniotic sac for both fetuses – MC-MA twins (1-2%).

In our days, twin births represent 30‰ of all births in Portugal. Twin gestation is a high risk pregnancy whose successful outcome depends on timely diagnosis of several maternal or fetal problems.

In this thesis, we try to establish the best sonographic measurements to identify twin pairs with an intertwin weight discordance >25%, we analyze the benefit of changes in BMI to mothers carrying DC twins, and we evaluate the risk factors and the outcomes of twin pregnancies with gestational diabetes mellitus.

However the main goal of this work is to determine the optimal time of delivery for an uncomplicated twin gestation, the safety of labor induction and the puerperal morbidity of cesarean (CS) delivery in twins.

Current recommendations suggest the optimal time of delivery for DC twins is at 37-38 wks, at 36-37 wks for MC-DA twins and at 32-34 wks for MC-MA twins.

A vaginal delivery could be considered for vertex-vertex twins and vertex-non vertex twins, when the provider’s skills and experience allow, and is safe in MC-DA twins. Protocol for induction of labor used in singletons is applicable in twins and misoprostol is safe for labor induction. A Cesarean section is recommended in MC-MA, non - vertex presenting twins, when the second twin is ≥40% larger than the presenting twin and women with a uterine scar. Patients should receive thorough information about the risks of vaginal and CS deliveries and the vaginal route should be performed by a medical team with experience in obstetric maneuvers

Chapter I. Introduction

I.Introduction

When I first began my fellowship at Maternidade Dr. Alfredo Da Costa (MAC), in 1987, and for the six years that followed, twin pregnancies were handled in the High Risk Outpatients Clinic using the same protocol as employed in singleton pregnancies. This entailed evaluations every month until 36 weeks, and evaluations every two weeks thereafter, awaiting spontaneous delivery or scheduled cesarean at 41 weeks. Chorionicity was unknown in most cases. Ultrasound was performed only once every trimester, premature delivery occurred frequently and adverse outcomes were many.

Several cases made a particular impression on me. A medical doctor, my age and living in my neighborhood, was followed at MAC throughout her whole pregnancy, which resulted in a stillbirth at 40 weeks of gestation and a survivor twin girl who was later diagnosed with cerebral palsy. An infertile patient, pregnant with triplets resulting from In Vitro Fertilization, delivered at 26 weeks with three neonatal deaths; no one had looked at her cervix during her whole pregnancy. A patient with spontaneous twins was hospitalized due to premature labor at 34 and delivered one week later: a stillbirth girl and a livebirth boy, one thousand grams heavier than his sister.

Some of the unfavorable outcomes were the result of lack of experience or a poor interpretation of signs during the pregnancy. I ended my fellowship believing that a personalized consultation could substantially improve the results of this type of high risk pregnancy.

In 1994, I asked for permission to start a Twin Outpatient Consultation. Most of the barriers I hit were bureaucratic: no suitable location, no available nurses, and probably not enough cases to warrant the effort. Thankfully, I was supported by Dr. Dória Nóbrega, the person in charge of the Obstetrics Department, and in September 1994 I began following the first twin pregnancy, now labeled with two blue circles in the patient's file. Twin pregnancies were followed in the same place as the High Risk Outpatients Consultation, with the same nurses. They were now, however, channeled to and followed by me.

From the start, new protocols were implemented. Patients with twin pregnancies were evaluated every month until the 22-week mark, every fortnight until 32 weeks and weekly thereafter. Cardiotocography started at 32 weeks or earlier, if there were complaints of contractions. Ultrasound was performed every three weeks after 22 weeks and even more frequently in monochorionic twin pregnancies. Patients were carefully informed of warning signs and advised to stop working at around 20 weeks, depending on the patient's occupation. Digital evaluation of the cervix was performed every consultation, and bed rest or even hospitalization was advised in high risk scenarios. Patients were allowed to show up without appointement if something felt wrong, and were strongly advised to go to the emergency unit if any of the warning signs were detected. Triplets or higher order twins were hospitalized at around 26 to 28 weeks.

In 1995 we performed our first evaluation, comparing 36 twin pregnancies followed in the Twin Consultation (study group) to 45 patients (control group) who only delivered at MAC. Four (10.5%) patients in the study group had had previous preterm deliveries with no survivor newborns. The average gestational age at delivery was 36 weeks and 6 days in the study group, compared with 34 weeks in the control group. In the study group, only four cases had a gestational age at delivery less than 35 weeks, and only two twins from one patient with a unicorn uterus who delivered at 23 weeks did not survive.

After this first evaluation, we were confident our protocol was working, but ever since we have not stopped checking our outcomes every year, trying to understand the setbacks that occurred and how they could have been avoided. Throughout all these years, we always held the belief that more than the immediate obstetric results, the truly important outcome of the obstetric care was the children's wellbeing, and we worked with the pediatric team to evaluate the childern's sequels.

Today, almost 20 years later, we have followed and delivered 2210 twin gestations, and hold the largest twin pregnancy database from a single care Center. We have given numerous oral and poster presentations, and published several articles on the subject of twin pregnancy. Our papers are cited in the Guidelines of the Royal

College of Obstetricians and Gynaecologists (2008) and in UpToDate (2014). We are proud to have contributed to MAC being recognized as a top care center for multiple gestations.

Chapter II. Twin Pregnancy In Perspective

II.Twin pregnancy in perspective

1. Definition

Twins occur when more than one offspring is produced in the same pregnancy.

Twins can develop from one single zygote when during the first two weeks the early embryo splits into two or more parts that subsequently develop separately, giving rise to two or more individuals. These types of twins are called monozygotic (MZ) twins and are phenotypically very similar.

The second type of twins results from a mechanism of poly-ovulation, with the growth in the same cycle of two or more ovulatory follicles and with subsequent multiple fertilization. Because they were originated from different zygotes they are called dizygotic twins (DZ). This kind of twins always has two placentas and two amniotic sacs, and because of that we call them dichorionic-diamniotic twins (DC-DA). They are as phenotypically similar as brothers from different gestations.

In humans, the frequency of MZ twins is relatively constant, ranging from 3.5 to 5.0 per thousand, and corresponds to about one third of the number of DZ twins. In 18% to 36% [1] of the cases MZ twins are also DC-DA and, from a clinical point of view, present the same problems as DZ twins. In 60 to 70% of the cases they have the same placenta and two amniotic sacs – monochorionic-diamniotic twins (MC-DA) –, and in less than 1% they have the same placenta and the same amniotic sac – monochorionic-monoamniotic twins (MC-MA). Finally, a rarer kind of MZ twins, conjoined twins, is characterized by a connection between the bodies of the twins that can be slight or extensive.

2. Epidemiology

According to Smiths et al [236] the average of the national twinning rate using the records of 76 countries is 13.1 per 1000, or one twin birth in 76.3 births. However twinning rates vary considerably around the world, with ethnicity [2]. Natural twining rates are high in some African countries (17 and more per thousand), low in East Asia and Oceania (less than 8 twins per 1000 births) and have an intermediate rate (9-16 per 1000 births) in Europe, United States of America (USA) and India.

The rate of monozygotic twinning is relatively constant (4 per 1000 live births), regardless of maternal age, race, or parity, although genetic predisposition may have some influence. Therefore, differences in twining rates among countries and over time are mostly due to variations in DZ twins.

There are several factors associated to DZ twining: maternal age being the first one. The incidence of DZ twins increases with maternal age, up to 35-39 years, and declines thereafter. This increase has been related to the rise in the secretion of gonadotrophins with age, with maximum stimulation of follicles at ages 35-39 and subsequent decline in ovarian function at older ages [3]. Since the middle of the 1970s, the proportion of births to women in their thirties has risen steadily. In 1987, 20% of all births involved women aged 30 to 34, which represents 75% more than the comparable proportion in 1971 (11.4%).

In the United States of America (USA), between 1980 and 2006, twin birth rates rose 27% for women <20 years compared with 80% for women in their 30s and 190% for women with more than 39 years of age. In 2006, 20% of births to women ≥45 years old were twins, compared with 2% of births to women 20-24 years old [7]; so maternal age is one of the most important reasons for the rise in DZ rates in the last decades. Since 1990, in the USA, the rates of twin pregnancies in women >40 years have risen 57% for non-Hispanic white women, 38% for non-Hispanic black women and 21% for Hispanic women [10], as shown in Figure 1.

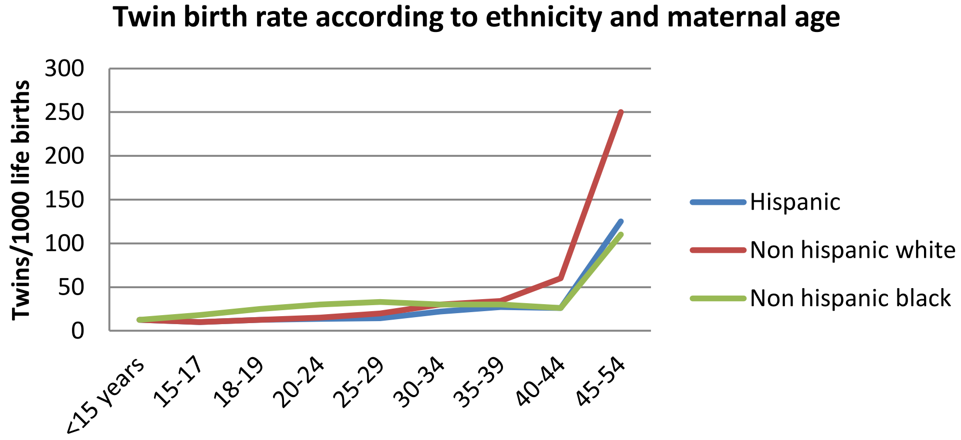


Figure 1 - Twin birth rate: based on maternal ethnicity and age.

Adapted from: Chauhan et al.[10] *Twins: prevalence, problems, and preterm births.* Am.J. Obstet Gynecol 2010; 203:305-315

Bamberg et al. [81], analyzing a cohort of 1,239 twin pregnancies delivered >24 weeks (wks), observed that 813 (65.6%) resulted from spontaneous conception and 426 (34.4%) from infertility treatment, finding that the mean maternal age was statistically significantly higher in the fertility treatment patients compared with the spontaneous group (32.5 ±5.1 versus 30.1 years ± 5.6, respectively; P<.001) and that the overall mean maternal age in the entire cohort increased over a 10-year period (January 1998 to October 2008) from 29.6 years to 32 years, with a statistically significantly higher increase observed in the fertility group, from 30.7 to 33.9 years. The rate of women aged >35 years was statistically significantly higher in the fertility than in the spontaneous group [37.6% versus (vs) 22.9%, respectively, P<0.001].

When they evaluated the linear distribution of the entire collective, they identified an increase in twin deliveries from 100 per year in the beginning of the 10-year observation period to more than 120 at the end of it, attributable to a statistically significant increase in infertile mothers, while the rate remained fairly constant in spontaneous pregnancy mothers. In the fertility group, the number of twin deliveries in the year 2007 was more than twice that observed in 1998 (53 vs. 22), as shown in Figure 2.

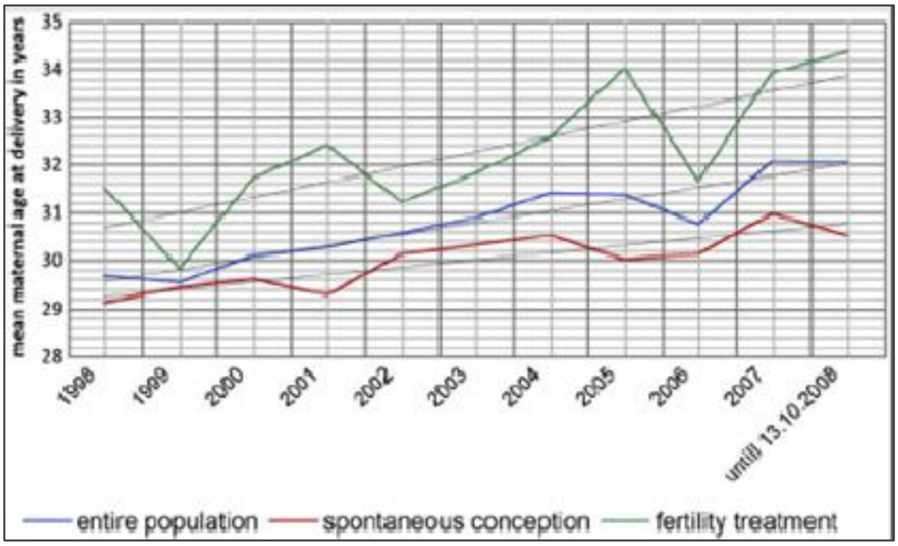


Figure 2 - Mean maternal age by mode of conception.

Adapted from Bamberg et al. [81]. *Maternal characteristics and twin gestation outcomes over 10 years: impact of conception methods*. Fertil. Steril.2012; 98:95-101

Two studies reported that twin pregnancies account for approximately 1.5% of spontaneous pregnancies, but account for 15% to 30% of medically assisted pregnancies [82, 83]. Bamberg et al. [81] found a higher value of 34.4%, which is comparable to the value reported by Pinborg [84].

Pinborg et al. [84], analyzing a large Danish cohort study encompassing more than 10,000 twin gestations, also found a statistically significantly higher maternal age in twin gestations after fertility treatment.

However, maternal age might not be the only factor of relevance. Kleinhaus et all [238] looked at 1,115 sets of twins, 22 of triples and 1 of quintuplets, collected from a cohort of 92,408 offspring born in Jerusalem between 1964 and 1976, and showed an association of increasing paternal age with the increase in incidence of twin deliveries, independently of maternal age.

Maternal height and maternal obesity are also risk factors in twining rates [4]: a report [5] from a Danish population indicates that twins are more common in obese than non-obese women. Reddy et al. [4] reported a statistically significant trend for increased risk of total twining with increasing BMI ($p<0.001$). The odds of MZ twining were not significantly related to BMI, but the odds of DZ twining were significantly related to the increased of BMI, as shown in Table1.

Table 1 - Twinning as a function of BMI and zigosity.

Adapted from: Reddy et al.[4] *Relationship of maternal body mass index and height to twinning.* Obstet Gynecol 2005:105:593-597

BMI(kg/m^2)	Total(n)	Twin Pregnancies N (%)	Crude OR(95%CI)	Adjusted OR(95%CI)*
MZ twins				
<20	12,924	47 (0.4%)	Reference	Reference
20-24.9	27,069	100(0.4%)	1.02(0.72-1.44)	1.01(0.71-1.44)
25-29.9	8,019	28(0.3%)	0.96(0.72-1.53)	0.91(0.56-1.47)
≥30	3,399	14(0.4%)	1.13(0.62-2.06)	1.05(0.56-1.95)
DZ twins				
<20	12,923	46(0.4%)	Reference	Reference
20-24.9	27,091	122(0.5%)	1.26(0.90-1.77)	1.17(0.83-1.65)
25-29.9	8,047	56(0.7%)	1.96(1.32-2.89)	1.51(0.99-2.29)

*Adjusted for maternal race, age, parity and height (in cm)

There has been a marked increase in obesity [6] around the world, with the proportion of women in the USA aged 20-39 years with BMI of 30 or more increasing from 9.3% in the early 1960s to 29% in 1999-2002; so overweight and obesity could be another reason for the rise in the spontaneous twin's rate.

High parity, heavier smoking and the previous use of oral contraceptives are others factors that increase the DZ twining. In this kind of twins it is also recognized that a hereditary component in the female line could explain the higher rate in some families over generations.

However, the major new factor in twining during the last decades was the introduction and fast increase in the use of assisted reproductive technologies (ART) such as ovulation induction (OI), intra-uterine insemination (IO) and *in vitro* fertilization (IVF).

OI is used in women with oligo or anovulation, usually using drugs such as clomiphene citrate or gonadotrophins, and more than the target ovulation of a single oocyte may result from this treatment. Superovulation (SO) is used in ovulatory women with age-related or unexplained sub-fertility, and can also result in a multiple gestation. Twins or high order pregnancies can happen with ART when multiples embryos are transferred to maximize the probability of pregnancy. However, there is a consensus [7] that the majority of twin births results from natural conception (60%), with OI/SO and ART treatments accounting proportionally for the remainder (OI/SO: range 21% to 32%; ART: range 8% to 16%). Pinborg et al. [84] notice that, in Denmark, one-third of twin pregnancies are now a result of IVF or ICSI treatment.

According to our database, out of 1,599 twins followed and born at Maternidade Dr. Alfredo da Costa (MAC), 1,199 (75%) resulted from spontaneous pregnancies; 85(5.3%) from OI and 315 (19.7%) from IVF or ICSI, figure 3

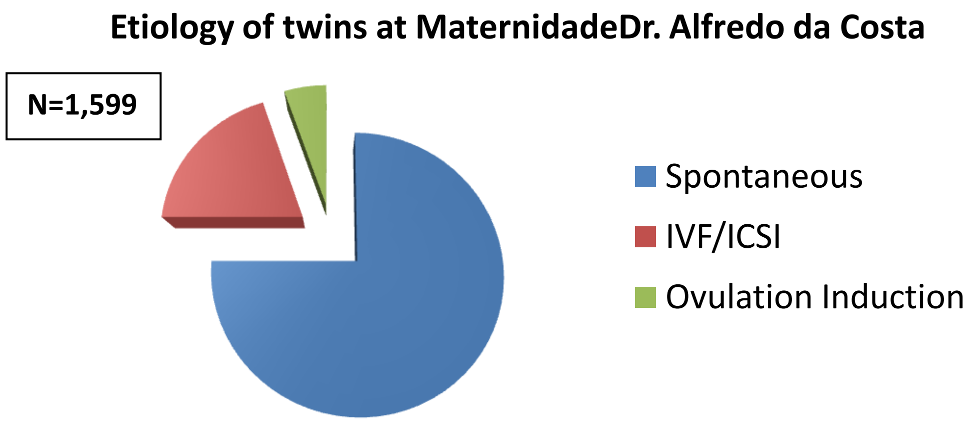


Figure 3 - Etiology of twins at Maternidade Dr. Alfredo da Costa (1994-2012)

The risk of MZ twins may also be increased by assisted reproductive technology (ART), two fold in conventional IVF cycles [8] and 24-fold in cycles involving micro-injection (ICSI) and extended culture of the embryos to the blastocyst stage [9]. In our database, we have observed that 32/472 (6.8%) MC twins resulted from infertility treatment (OI and FIV/ICSI).

The number of live twin births and the ratio of twin births per thousand total live births have risen fairly steadily since the early 1970s. In the United States, between 1980 and 2006, the twin rate climbed 101% [10], as seen in Figure 4. The twin's rate has also increased elsewhere. In Australia [19], infants of multiple births in the Intensive Care Units admissions, increased from 24,6% in 1994 to 30,6% of 2005; the contribution from spontaneous multiple birth remained stable, whereas the percentage of multiple pregnancies from assisted conception increased gradually from 4,6% in 1994 to 10.3% in 2005 (p<0.001).

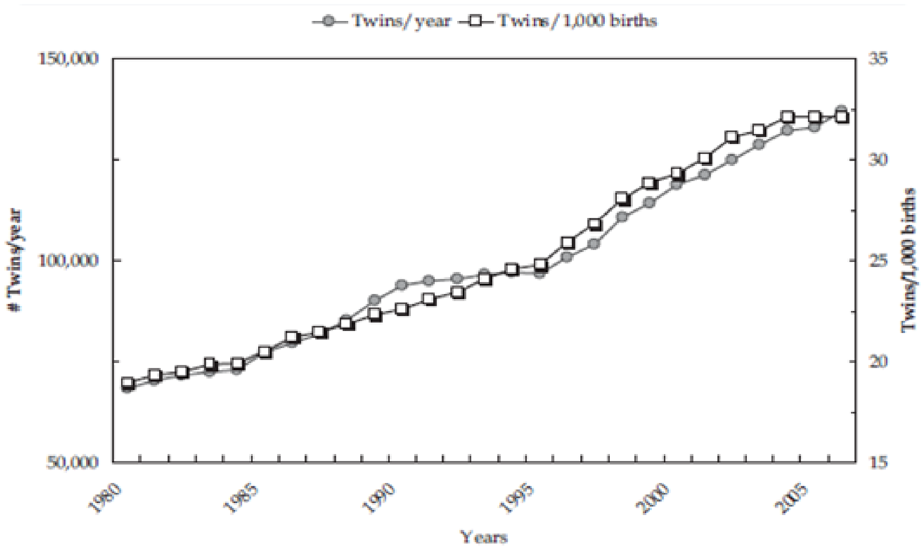


Figure 4 - Twin deliveries and birth rate: United States 1980-2006

Adapted from: Chauhan et al.[10] *Twins: prevalence, problems, and preterm births.* Am.J.Obstet Gynecol 2010; 203: 305-315

In Spain, the available information [88] shows that in the last 20 years the number of multiple births of twins has more than doubled (75 out of every 10,000 births in 1980 to 175 out of every 10,000 in 2004) and the number of triplets has increased six-fold (11 out of every 10,000 births in 1980 to 60 out of every 10,000 in 2004). In Spain during 2003, 3,080 twin births and 286 triplet births were attributed to ART [89].

In our database 44/92(48%) of the triplets followed and delivered at MAC have resulted from IVF or ICSI treatment, 12/92 (13%) from IO and only 36/92 (39%) from natural conception. Overall, 61% of our triplets have resulted from some kind of infertility treatment, as shown in Figure 5.

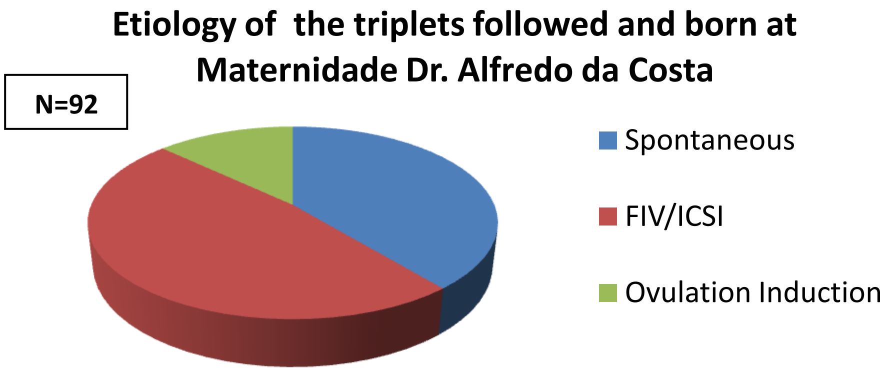


Figure 5 - Etiology of triplets at Maternidade Dr. Alfredo da Costa (1994-2012)

Approximately 1% of infants born in the USA in 2006 were conceived with the use of ART [10]. From those infants, 48% were multiple birth deliveries [10]. When the International Committee for Monitoring Assisted Reproductive Technology analyzed the ART results for the year of 2002, coming from 53 countries [142], for conventional IVF and ICSI, the overall twin rate was 26%. Twin rates were of 32% in the USA, 25% in Latin America, 23% in Europe, 22% in Asia and the Middle East and 21% in Australia and New Zealand.

Several factors contribute to the increased incidence of multiple gestations resulting from infertility treatments: competitive pressures to apply ovulation induction or IVF early to achieve high pregnancy rates for clinic advertising purposes; the economic pressure on patients restricting the number of ART cycles they can attempt, and pressure from infertility couples to transfer more than one embryo, to improve the chances of pregnancy and to obtain two or more babies with a single treatment.

Finally, Steinman [225] reported that insulin-like growth factor present in dairy products may increase the chance of DZ twinning. Vegan women (who exclude dairy from their diets) are one-fifth as likely to have twins as omnivore or vegetarian women. He concluded that genotypes favoring elevated IGF, and diets including dairy products, especially if growth hormones have been given to cattle, appear to enhance the chances of multiple pregnancies due to ovarian stimulation.

3. Maternal problems of twin pregnancies

A. Preterm delivery

Compared with singleton pregnancies, twins are associated with an increased incidence of complications during gestation; preterm delivery is the most common [10]. The chances of having a newborn with a weight <1500 g is 10 times greater in twin pregnancies compared to singletons [16], and at least 50 to 60% of all twins are born before 37 weeks. Twins account for 15% of all preterm births in the United States and prematurity contributes substantially to perinatal morbidity, mortality, and to the costs of multiple pregnancies. Lukassen et al. [141], evaluating the cost in Euros (€) of 135 singletons and 144 twins pregnancies after IVF, found that the mean cost per twin pregnancy was significant higher when compared with singleton pregnancy (p<0.001), causing a greater than €10,000 difference in costs, table 2.

Table 2 - Cost in Euros per singleton and twin pregnancy after IVF.

Adapted from: Lukassen et al [141] *Cost analysis of singleton versus twin pregnancies after in vitro fertilization.*Fertil. Steril. 2004;81:1240-1246.

	Singleton pregnancy	Twin pregnancy	Difference
Delivery cost (€)	553	700	187
Hospital care mother(€)	1,113	3,147	2,034
Neonatal care including NICU(€)	755	9,534	8,779
Total(€)	2,549	13,469	10,920

In 2008, we evaluated the costs of the 155 multiples followed and born at Maternidade Dr Alfredo da Costa [150] throughout 2007. For each live baby the total costs for the twins (n=288) were €5,904; €10,046 for each triplet (n=27) and €83,717 for each quadruplet (n=4), with most of the cost arising due to neonatal care following prematurity. Looking to our 144 twin pregnancies, MC twins and spontaneous pregnancies were the more expensive, as shown figure 6.

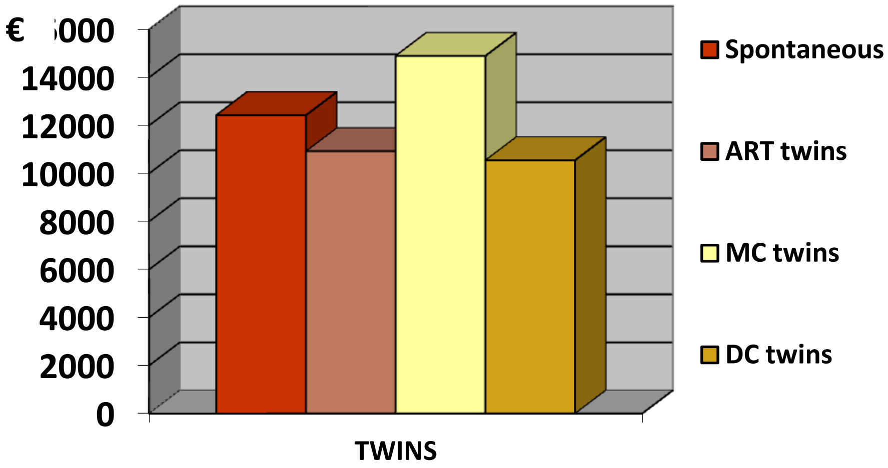


Figure 6 - Costs for Multiple Pregnancies and their Newborn (MAC-2007)

Adapted from: Simões e al.[150] Costs for multiple pregnancies and their newborn .11th World Congress on Controversies in Obstetrics Gynecology and Infertility Paris-2008- Poster

In 2006, Martin et al. [12] published a study noticing that among the 137,085 twins delivered in the USA, approximately 60% were preterm (78,824 infants) and weighed <2500 g (82,799 infants); approximately 1 out of 10 twins was born at <32 weeks of gestation (n = 16,597 infants) or weighted <1500 g (n = 13,983), as depicted in figure 7.

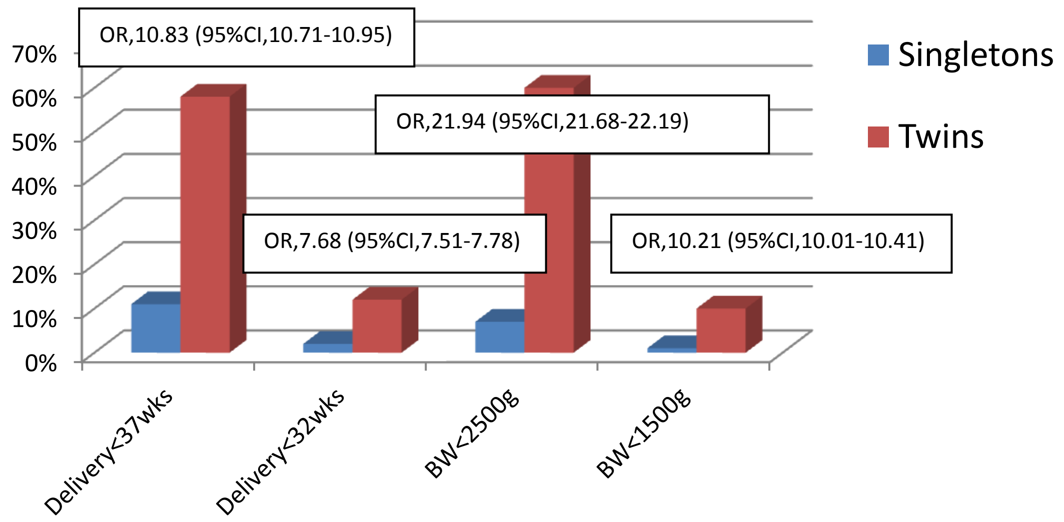


Figure 7 - Preterm Birth in 2006: Twins versus Singletons.

Adapted from: Chauhan et al. [10] *Twins: prevalence, problems, and preterm births.* Am.J.Obstet Gynecol 2010; 305-315 and Martin JA et al. [12]. *Births: final data for 2006.* Nati Vital Stat Rep. 2009; 57:1-102

Ananth et al. [17] found that the death rate for twins was 3 times higher than for singletons, and that severe handicap in very low birth weight survivors of twin pregnancies occurred two times more frequently than in very low birth weight survivors of singletons pregnancies.

However, Garg et al. [19], comparing the perinatal characteristics, neonatal morbidity and mortality of 10,080 infants, 7,304 preterm singletons, 2,444 twins and 320 triplets born at 22-31 weeks of gestation, admitted to neonatal intensive care units in New South Wales and Australian Capital Territory, between 1994 and 2005, found that the major neonatal morbidities were similar between the three groups, while twins of 22-27 weeks' gestation had higher mortality compared with singletons. Nevertheless, mortality only diverged below 24 weeks, at the very extreme of viability. They also found that mortality was predicted by decreasing gestational age, male gender and lack of antenatal steroids, whereas preterm infants following assisted conception (IVF, ICSI) had better survival rates in neonatal intensive care unit (NICU). They concluded that using a multivariable regression model, plurality was not a risk factor for mortality in the overall group, figure 8.

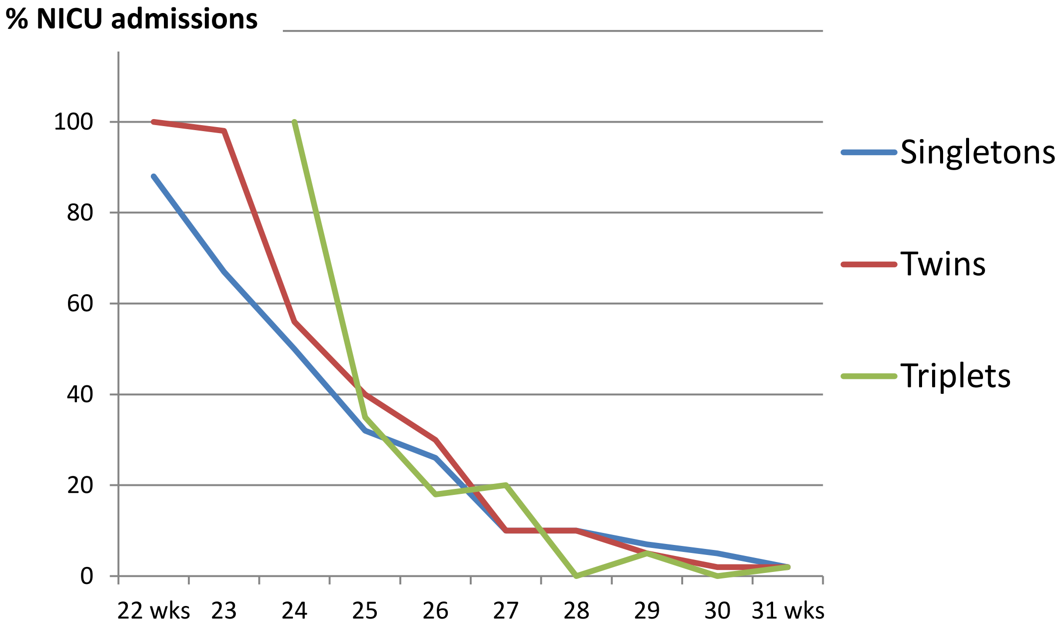


Figure 8 - Gestational age-specific mortality for twins, singletons and triplets. NICU.

Adapted from: Garg et al.[19] *Perinatal characteristics and outcome of preterm singleton, twin and triplet infants in NSW and the ACT, Australia (1994-2005).* Arch. Dis. Child Fetal Neonatal Ed 2010; 95:20–24.

Dickey et al. [85] reported that, for twins, maternal height was inversely associated with the risk of preterm births. Maternal height ≥ 176 cm was associated with a 14% reduction in the overall preterm birth. Conversely, maternal weight (especially >90 kg) and higher BMI was associated with an increased risk of preterm births. In particular, obese women (BMI > 30 kg/m^2) were at markedly higher risk of having very early preterm (<28 weeks) and very preterm birth (< 32 weeks). Very obese women (BMI > 35 kg/m^2) have a more than threefold increased risk of very early preterm birth, and a twofold increased risk of very preterm birth. They concluded that, for twin pregnancies, the risk of very preterm birth was >10% when weight was ≥90 kg or when BMI was ≥35 kg/m^2. More importantly, the risk for twins of very early preterm birth, the period of highest risk for neonatal mortality and developmental disability, was 4.8% when weight was ≥90 kg and 6.1% when BMI was ≥35 kg/m^2.

Nicolaides et al. [143] claimed that in twin pregnancies, as in singletons, the risk of spontaneous preterm delivery before 33 weeks can be predicted from measurement of cervical length (CL) at 23 weeks of gestation. The risk increases gradually from about 2.5% at 60 mm to 12% at 25 mm and exponentially below this length, to 17% at 20 mm and 80% at 8 mm, figure 9. They also noticed that measurement of cervical length provides sensitive prediction of spontaneous early preterm delivery. Thus, cervical length of 20 mm or less is found in about 8% of the population and this group contains about 40% of women delivering spontaneously before 33 weeks. The results of this study confirm other previous reports [144,145,146].

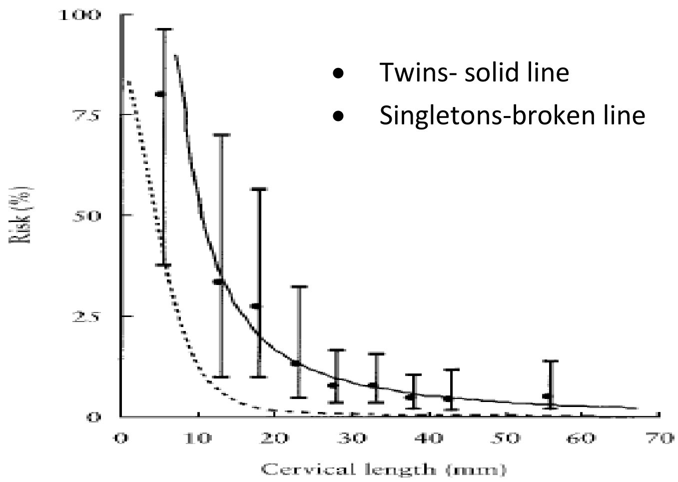


Figure 9 - Rate of spontaneous delivery before 33 weeks according to cervical length at 23 weeks of gestation.

Adapted from: Nicolaides et al.[143] *Prediction of preterm delivery in twins by cervical assessment at 23 weeks.* Ultrasound Obstet Gynecol 2001;17:7-10

In 2010, Conde-Agudelo et al. [147] published a meta-analysis including twenty-one studies (16 in asymptomatic women and 5 in symptomatic women) with a total of 3,523 women with twin pregnancies. This systematic review and meta-analysis gives the strongest evidence to date that transvaginal sonographic measurement of CL at 20-24 weeks of gestation is a good predictor of spontaneous preterm birth in asymptomatic women with twin pregnancies. A CL <25 mm predicted spontaneous preterm birth at <32 and <34 weeks of gestation, whereas a CL<20 mm predicted preterm birth at <28 weeks of gestation. A “normal” CL, however, was less accurate in predicting the absence of preterm birth. In addition, transvaginal sonographic CL has limited accuracy in predicting spontaneous preterm birth in women with twin pregnancies and threatened preterm labor, and in asymptomatic women in whom the test was performed after 24 weeks of gestation.

Liem et al. [234] in a systematic review and meta-analysis published in 2013 reported limited evidence on the accuracy of cervical length measurement testing the prediction of preterm birth in symptomatic women with a twin pregnancy especially on the most important outcome, the delivery within 7 days.

In one evaluation we performed in 2008, we attempted to find the risk factors for preterm delivery in our population of twin pregnancies [48}. Twins with an elective termination before 36 weeks were excluded. A total of 605 twin pregnancies were considered. The study group consisted of 208 (34.4%) twin pregnancies with spontaneous delivery before 36 weeks. The remaining 397 pregnancies delivered at 36 weeks or later, formed the control group. Twenty nine (3.8%) of the twins from the study group were delivered before 32 wks, and 5 (0.8%) before 28 wks. Using a multiple logistic regression, we found that: the presence of a malformed fetus, an obstetric history of preterm delivery, more than three abortions, preterm contractions, Intrauterine growth restriction (IUGR) of any twin, low maternal height and nulliparity, all constituted risk factors for preterm delivery, as shown in table 3.

Table 3 - Risk factors for preterm delivery in twins.

Adapted from: Lima et al.[148] Risk *factors of preterm delivery in twins.* Acta Obstet Ginecol Port. 2008; Suppl 1; 481

Risk factors	p	Odds Ratio	95%CI
Fetal Malformations	0.006	18.074	2.270-143.892
Obstetric History*	0.032	4.650	1.141-18.945
Threatened Preterm Labor	<0.001	2.658	1.849-3.819
IUGR	0.035	2.152	1.057-4.380

*Previous Preterm delivery, IUGR and /or >3 miscarriages

B. Hypertensive disorders

Twin gestations lead also to an increased risk of hypertensive disorders, the incidence varying between 13 to 37%. Krotz et al. [20] found that the range of relative risk of gestational hypertension, preeclampsia and eclampsia for twins, compared to singleton gestations was 1.2 to 2.7, 2.8 to 4.4 and 3.4 to 5.1 respectively. Parity, African-American ethnicity, and young maternal age were all factors that increased the relative risk of developing hypertensive disease to 4.0, 1.8 and 1.5 in mothers of twin gestations. Factors such as: maternal smoking, income level and zygosity had a negligible effect on the relative risk of acquiring hypertensive disease in twin gestations. Mothers of twins also exhibited an earlier onset of hypertensive disease comparatively to singletons.

Analyzing our database, we found 284 (18.2%) cases with hypertensive disorders, among 1561 twins. From another evaluation of the risk factors of hypertensive disorders in twin gestation [152], we found that 185 (18.8%) among a cohort of 983 twin gestations, presented hypertensive disorders. 12.6% (n=124) had gestational hypertension, 3.8% (n=37) had preeclampsia (PE) or HELLP syndrome, and 2.4% had chronic hypertension. We found an association between hypertensive disorders and maternal age>35 years (p=0.036), obesity (p=0.019), cholestasis (p=0.032), gestational diabetes (p=0.004) and discrepancy ≥ 25% (p=0.041). Nulliparity and monochorionicity were risk factors to PE and HELLP syndrome while advanced maternal age, obesity and ART were risk factors for gestational hypertension. Delivery at 32 weeks or later was a risk factor to gestational hypertension and PE/HELLP. In the logistic regression model, advanced maternal age, obesity and gestational diabetes were independent risk factors to hypertensive disorders in twin pregnancies. Monochorionicity and nulliparity were independent risk factors to PE/HELLP. Finally, delivery with at ≥32 weeks was an independent risk factor to gestational hypertension.

C. Gestational diabetes

Compared with singleton pregnancies, patients with twins had a two-fold increased risk of developing gestational diabetes (GDM) [10,15]. The incidence ranges between 5 to 8% and in terms of neonatal outcome, twins of gestational diabetes mothers had a higher rate of admission to the NICU, longer hospitalization, and higher risk of respiratory distress syndrome (RDS). The hyperglycemia associated with pregnancies of diabetic women has the potential for producing adverse outcomes by two mechanisms [21]. The first is by asymmetric growth enhancement, which may lead to large-for-gestational-age fetal growth and macrosomia, which in turn predisposes to intrapartum complications that may be associated with birth trauma or an increased risk of cesarean delivery. The second mechanism may operate through the metabolic effects of hyperinsulinemia, with resultant increased oxygen demand that may lead to fetal hypoxia and acidemia [22]. This effect of hyperglycemia has been associated with an increased intervention rate for non-reassuring antenatal testing, as well as an increased rate of fetal death and perinatal loss. In twins, the growth enhancing consequences of GDM are unlikely to produce intrapartum mechanical problems because most pregnancies are delivered before term and the individual fetal weights and sizes are not large. However, the potential for hypoxemia and acidemia caused by the metabolic effects of hyperinsulinemia may be of significance if superimposed on twin pregnancies associated with either intrauterine growth restriction or discordance resulting from placental insufficiency of vascular origin or both and may increase the risks for adverse outcome.

Analyzing our database, we found 152 (9.7%) cases with diabetes among the 1561 twin pregnancies.

D. Intrahepatic cholestasis

Intrahepatic cholestasis of pregnancy is a relatively uncommon condition in singletons that is associated with significant fetal risks, including preterm delivery, meconium staining, neonatal respiratory distress syndrome, and intrauterine fetal death [30]. The incidence varies widely according to geographic location and season, being more common in the winter months in Chile, Finland, Sweden, and Portugal [31]. The incidence of cholestasis in the United States is reported to vary from 0.3% to up to 5.6% of pregnancies in a Latina-rich population [32].

We have found an incidence of 3.5% of cholestasis in our database. However, intrahepatic cholestasis of pregnancy has been reported in 20–22% of twin deliveries in Chile [33].

In addition to environmental factors and genetic predisposition, elevated estrogen levels are postulated to play a role, as evidenced by the observation that intrahepatic cholestasis of pregnancy is more common in multiple gestations. Several gene mutations have been implicated in intrahepatic cholestasis of pregnancy, particularly those controlling hepatocellular transport systems [30]. For example, the *ABCB4* gene, which encodes multidrug resistant protein 3, is thought to be involved in progressive familial intrahepatic cholestasis. Hormonal influence, with rising estrogen and progesterone levels in the third trimester, in vitro fertilization, decreased dietary intake of selenium, and infection are also thought to play a role in the etiology of intrahepatic cholestasis of pregnancy. Although the onset of intrahepatic cholestasis of pregnancy is typically during the second half of pregnancy, it has been reported as early as the 10th week of gestation.

Pruritis, particularly in the palms and soles, is the most common symptom. Dermatologic examination in patients with intrahepatic cholestasis of pregnancy, however, is usually normal, with the exception of excoriation marks secondary to pruritis [32]. Increasing increments of total bile acids are thought to correlate with adverse outcome. The probability of fetal complications includes spontaneous preterm delivery, asphyxial events, and meconium staining increase by 1% to 2% per additional µmole/L of serum bile acids. A bile acid level of 40 µmoles/L or higher is thought to be a poor prognostic indicator. However, primary dermatologic findings may be present in some patients with intrahepatic cholestasis of pregnancy and it is important to consider to differential diagnose other dermatologic conditions as PUPPP Syndrome.

E. Pruritic urticarial papules and plaques of pregnancy (PUPPP Syndrome)

Pruritic urticarial papules and plaques of pregnancy (PUPPP) are among the most common pruritic dermatoses observed in pregnant women. PUPPP appears most frequently in the third trimester, in primigravidas, and in multiple gestation pregnancies [34]. The eruption of changes occurs initially on the abdomen and extends over the thighs, legs, back, buttocks, arms, and breasts, Figure 10. Skin changes typical for PUPPP are erythematous, urticarial plaques, and papules. Rash regression is usually observed within six weeks postpartum. Immunologic mechanisms, hormonal abnormalities, and abdominal skin distension have been suggested as etiologic mechanisms. PUPPP is thought to be harmless for the mother and fetus and usually requires intervention only for symptom relief. In some cases, laboratory investigation, histologic examination, and immunologic study should be performed to exclude more serious disorders of pregnancy, such as herpes gestationis or intrahepatic cholestasis of pregnancy.

Figure 10 - Pruritic urticarial papules and plaques of pregnancy in the abdomen (PUPP syndrome)

F. Excess weight gain

Another complication in twin gestations is excess weight gain. In 1990, the Institute of Medicine [60] defined optimal weight gain in twin pregnancies to be 35–45 pounds (15.9-20.4 kg) in a term twin pregnancy. Subsequent to these recommendations, a number of studies demonstrated that, similar to singleton pregnancies, gestational weight gain in twin pregnancies is positively associated with birth weight [61-63]. However optimal weight gain differs between different pre-gestational BMI. Based on this knowledge, the Institute of Medicine revised their recommendations for optimal weight gain in twin pregnancies in 2009 guidelines [64], recommending the following BMI-specific weight gains:

1. Normal-weight women (BMI 18.5–24.9 kg/m^2): 17–25 kg.
2. Overweight women (BMI 25–29.9): 14–23 kg
3. Obese women (BMI 30 or greater): 11–19 kg.
4. There was insufficient evidence to make recommendations for underweight women (BMI less than 18.5).

These recommendations were made assuming a term (37– 42 weeks) delivery. Fox et al. [65], from the analysis of a total of 297 patients with twin pregnancies and a recorded pre-pregnancy weight, maternal height, and maternal weight measurements during pregnancy, found that using the pre-pregnancy BMI, 16 (5.4%) women were underweight, 201 (67.7%) women were normal weight, 51 (17.2%) women were overweight, and 29 (9.8%) women were obese. The mean weight gain per week was 1.09±0.40 lbs (0.47±0.2 kg). In the entire cohort, the weight gain per week was significantly positively associated with the gestational age at delivery (Pearson correlation 0.152, P=0.009) and birth weight of the larger (Pearson correlation 0.239, P=0.001) and smaller twin (Pearson correlation 0.187, P=0.001). He concluded that women with twin pregnancies whose weight gain during pregnancy met or exceeded the revised 2009 guidelines had significantly improved pregnancy outcomes, including longer gestation, less overall preterm birth, less spontaneous preterm birth, and larger neonates.

Gonzalez-Quintero et al. [66], using a cohort of 5,129 twin pregnancies in women with normal, overweight or obese pre-pregnancy BMI found that the rates of spontaneous preterm delivery at <35 weeks were higher in all BMI groups for those with weight gain below guidelines, and that the numbers of pregnancies with both infants weighing >2500 g or >1500 g were significantly higher for women gaining weight at or above guidelines.

Chu et al. [67], analyzing data from women who delivered live, late preterm (34-36 weeks) and full-term (>37 weeks) singleton and twin infants (n=205,761) found that gestational weight gains were higher among mothers of twins compared with reported weight gains among mothers of singletons, and that better birthweight outcomes were associated with weight gains substantially higher among twin pregnancies than comparable weight gains for singleton pregnancies. They also found that women with a lower pre-pregnancy BMI show a higher weight gain during pregnancy than women with a higher pre-pregnancy BMI, as shown in Figure 11.

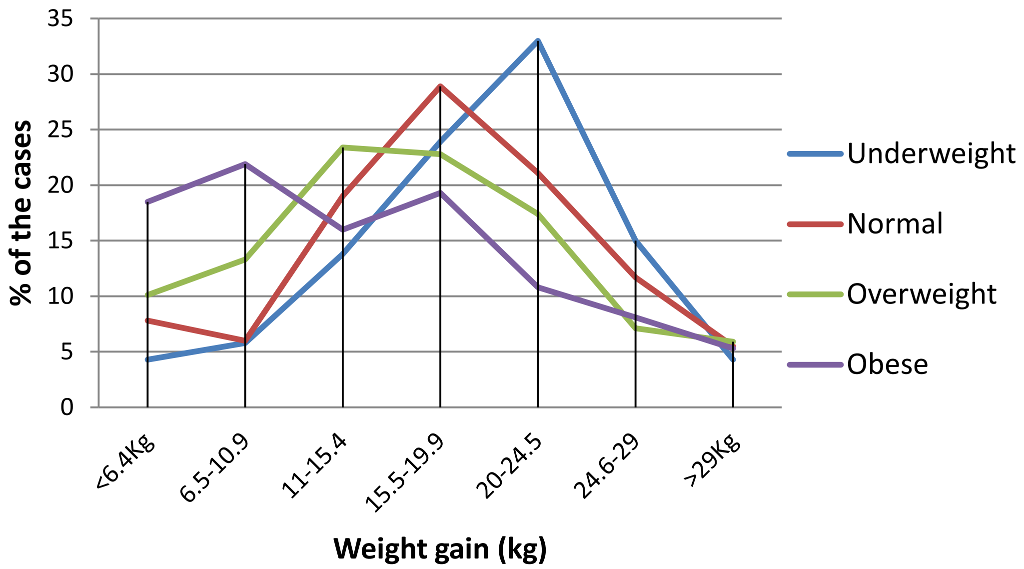


Figure 11 - Gestational weight gain by pre-pregnancy BMI among twins.

Adapted from: Chu et al [67]. *Gestational weight gain among US women who deliver twins, 2001-2006*. Am. J. Obstet Gynecol 2009;200:390.e1-390.e6.

These findings support the guidelines that a woman pregnant with twins should gain from 35 to 45 pounds (15.9-20.4 kg). However, they also found that birthweight outcomes continued to rise among mothers of twins who gained from 20.4 to 29 kg, Figure 12.

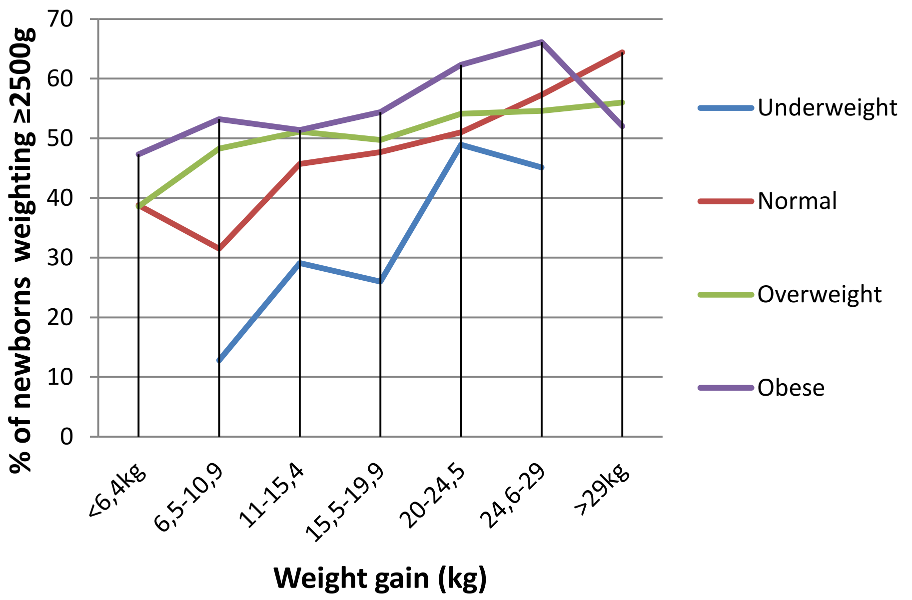


Figure 12 - Normal birth weight by gestational weight gain among twins.

Adapted from:Chu et al [67]. *Gestational weight gain among US women who deliver twins, 2001-2006*. Am. J. Obstet Gynecol 2009;200:390.e1-390.e6..

Findings from other studies show that higher gestational weight gains increased the risk of total complications during pregnancy and the rates of cesarean deliveries [68], so they concluded that given the high risk of obesity in the USA population, the benefits of higher gestational weight gains need to be balanced against the increased risk of weight retention and excessive body weight later in life [69].

Mochhoury et al [237] evaluated the impact of BMI before pregnancy and weight gain during pregnancy on the occurrence of maternal and neonatal morbidity in the Moroccan population, and found that the risks of moderate hypertension, macrossomia, dystocia and resort to CS were higher among overweight or obese women as well as among women pregnant of singletons whose weight gain was >16 kg.

We analyzed the influence of BMI in the prognosis of twin pregnancy [153]. From our database of 632 twin pregnancies, followed and delivered between 1994 and 2006, we define four BMI groups: BMI >30 kg/m^2 (n=55), BMI 25-29 kg /m^2 (n=141), BMI 20-24 kg /m^2 (n=351) and BMI<20 kg/m^2 (n=85). No significant differences were found with respect to maternal age between the four groups. However, hypertensive disorders (23.6% and 20% vs. 14.8% and 14%) and diabetes (14.5% and 10% vs. 3.4%

and 4.7%) had higher incidence in obese and overweight women, compared with the normal and underweight group (p<0.001). Obese women had the lowest rate of preterm delivery (16.4% versus 31.2%, 38.2% and 41.2%, p<0.001). Underweight women had the lowest rate of CS (p<0.001) and obese and overweight women had the highest rate of scar infections (1.8% and 0.7% vs. 0.3% and 0.0%, p=0.01), as shown in Figure 13.

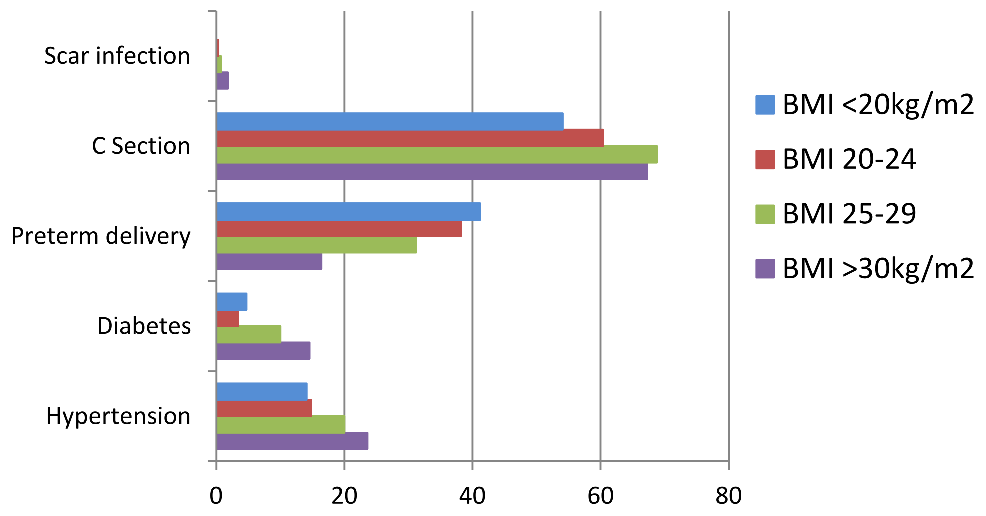


Figure 13 - Pregnancy and delivery problems according to BMI (MAC)

We performed another evaluation of the impact of maternal overweight and obesity in 1,191 twin pregnancies. From the total group of twin pregnancies, 29% were overweight or obese women and became our study sample. We found a positive correlation between overweight/obese and advanced maternal age (p=0.029), hypertensive disorders (p<0.001) and gestational diabetes (<0.001). We also found that the study group had a higher rate of babies that were large for the gestational age (p=0.014) and a higher rate of CS delivery (p=0.03). The rates of preterm delivery, small for gestational age (SGA) and respiratory distress syndrome (RDS) were similar to the rates found in our normal twin population.

G. Other maternal problems

Other complications of multiple gestations include **anemia, hyperemesis gravidarum, and exacerbation of pregnancy-associated gastrointestinal symptoms** such as reflux and constipation. **Chronic back pain, intermittent dyspnea, postpartum**

laxity of the abdominal wall, and umbilical hernias also occur frequently [7]. Usually problems increase with the number of fetuses [7], as seen in Tables 4 and 5.

Table 4 - Problems in multiple pregnancy.

Adapted from: Practice Committee of the American Society for Reproductive Medicin. [7] *Multiple gestation associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion.* Fertil .Steril. 2012; 97:825-834

	Singleton	Twin	Triplet	Quadruplet
Preeclampsia(%)	6	10-12	25-60	>60
Gestational diabetes(%)	3	5-8	7	>10
Preterm labor(%)	15	40	75	>95
Delivery at <37 wks(%)	10	50	92	>95
Delivery at <32 wks(%)	2	8	26	>95

Table 5 - Problems in multiple pregnancy.

Adapted from: Practice Committee of the American Society for Reproductive Medicin. [7] *Multiple gestation associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion.* Fertil. Steril. 2012; 97:825-834

	Singleton	Twin	Triplet
Prospective risk of fetal death (%)[a]	0.03	0.09	0.14
Gestational diabetes (%)	0.06	0.31	1.38
Neonates<2,500g (%)	6.2	53.2	93.2
Neonates<1,500g (%)	1.2	10.5	37.5
Average gestational age (wks)	39.1	35,3	32.2
Average birth weight (g)	3,358	2,347	1,687

[a]Prospective risk of fetal death between 24 and 43 weeks'gestation for singletons; at 41 wks for twins and at 38 wks for triplets.

Placenta previa, vasa previa, abruption placenta also occur more frequently in multiple gestations and **postpartum hemorrhage** complicates approximately 12% of multifetal deliveries [14].

Smithers et al. [86], in order to compare the obstetric and perinatal outcome of IVF and non-IVF twins and using the Perinatal Data Collection Unit registry of Victoria-Australia for the period (1991–1999), studied mixed-sex twins to ensure that only DZ twins were included in the study sample. There were 2,661 records of mixed-sex twins and they found that the perinatal mortality of IVF and non-IVF mixed-sex twins did not significantly differ. However, they noticed a global (IVF and non IVF twins) incidence of 4% of antepartum hemorrhage, 1.4% of placenta previa, 14% of premature rupture of membranes (PROM) and 61.5% of CS deliver with a risk of emergent CS of 19.5%, Table 6.

Table 6 - Rates of selected obstetric and perinatal outcomes in twins.

Adapted from: Smithers et al.[86] *High frequency of cesarean section, antepartum hemorrhage, placenta previa, and preterm delivery in vitro fertilization twin pregnancies.* Fertil Steril 2003; 3:666-668

Outcome	IVF group N=514(%)	Non IVF group N=2,067(%)	Odds ratio (95%CI)	P value
Placenta previa	11(2.1%)	15(0.7%)	3.08(127-7.46)	0.01
Antepartum hemorrhage	28(5%)	68(3%)	1.73(1.05-2.86)	0.03
PROM	83(16%)	247(12%)	1.20(0.89-1.61)	0.23
Elective CS	209(41%)	544(26%)	1.63(1.31-2.04)	<0.001
Emergency CS	119(23%)	321(16%)	1.28(0.99-1.66)	0.06
Birth<37 wks	277(54%)	928(45%)	1.27(1.02-1.56)	0.03

We compared [149] the obstetric outcome of twin pregnancies conceived by IVF (n=235) and ovulation induction (n=68) with those conceived spontaneously (n=997), and found, through univariate analysis, that patients who conceived with the assistance of IVF/ICSI had a significantly higher risk of being older (p=0.01), nulliparous (p=0.01), having hypertensive disorders (p=0.012), gestational diabetes mellitus (p=0.031), CS (p=0.008) and lower gestational age at birth, compared with the control group of spontaneous pregnancies. However, a multivariate analysis of the results regarding advanced maternal age (>35 years), chorionicity and obesity showed that patients who conceived with the assistance of IVF/ICSI only had a statistically significantly higher risk of gestational diabetes, Table 7.

Table 7 - Risk of obstetric complications comparing IVF twins with twins resulted from spontaneous conception.

Adapted from: Simões et al. [149] *Obstetric outcome of twin pregnancies conceived by IVF and ovulation induction compared with those conceived spontaneously* Acta Obstet Ginecol Port. 2012; 6:45-50

	p-value	**Odds ratio (95%CI)**
Diabetes	P=0.01	1.909(1.168-3.120)
Hypertension	P=0.938	1.011(0.669-1.329)
Cesarean section	P=0.130	1.313(0.923-1.868)

Parents of multiples are also affected **socially and psychologically**. Studies indicate that these parents are more likely to be exhausted, depressed, or anxious after the birth of the babies [87]. The difficulties of raising multiples may be further compounded if the children are physically or mentally disabled. In addition, parents may have little time for one another, which can further strain the couple's relationship. Parenting demands, financial demands, social isolation, and little time for one self may place a great deal of stress on parents of multiples. After a multiple birth, fathers may find it difficult to adapt to the new family context. This may be interpreted by the mothers as a lack of involvement. In such cases, the dialogue becomes difficult and can reduce marital satisfaction [89, 90, 91, and 92].

Roca de Bes et al. [89] analyzed mothers and fathers of children between 6 months and 4 years conceived by ART (n=123) using a sample divided into three groups: Parents of singletons (n =77), twins (n =37), and triplets (n=9). They found lower marital satisfaction in multiples families, no significant differences in depression but greater difficulty covering basic needs. These results suggested that not all psychosocial risks increase with multiple births however parents of multiples are at high risk of psychological illness.

4. Fetal problems in twin pregnancies

A. Fetal anomalies

Fetal anomalies are more frequent in twin gestations. The prevalence of cardiovascular anomalies is two times higher for twins when compared with singleton pregnancies, especially if they are MC twins [11] or are a result of ART. Because ART are often used in older women, twins from infertility treatment have a higher risk of aneuploidy.

Layde et al. [23], analyzing birth data from the state of Georgia (USA) between 1969 and 1976, and comparing twins vs. singletons, found an elevated incidence of encephalocele in same-sex twins ($p<0,05$). Analyses of the incidence of congenital malformations other than neural tube defects found that Tetralogy of Fallot and lung malformations were also more frequent in same-sex twins (0.04 and 0.009). Lung malformation was also more frequent in all twins compared with singletons ($p=0.004$). Lower gastro-intestinal defects were diagnosed more often in both same-sex twins ($p=0.000001$) and all twins ($p=0.00001$) than in singletons. Genital anomalies occurred more often in all groups of twins than in singletons, but the difference was only significant for the combined group of all twins ($p = 0.003$). Omphalocele /gastroschisis was substantially more frequent in both same-sex ($p=0.02$) and all twins ($p=0.01$) than in singletons. Two defects were more common in singletons than in same-sex twins: pyloric stenosis ($p=0.03$) and clubfoot ($p=0.04$).

Myrianthopoulos et al. [24] found more than twofold increases of cardiovascular and alimentary tract malformations in twins, as well as an almost 50% increase in central nervous system and related skeletal defects. Smithers et al. [86] found a 5.3% prevalence of birth defects in a sample of 2,661 DZ twins (5.6% of IVF DZ twins and 5.2% of non-IVF DZ twins). This difference was not statistically significant.

In some twin gestations we can have a **discordant anomaly**, where only one fetus is affected. Fetal structural anomalies affecting only one twin occur in >80% of instances [248,249]. However, the likelihood of an adverse outcome for the normal twin is increased. As we noted in our evaluation of risk factors of preterm delivery in twins [148], one abnormal twin was the major risk factor for preterm delivery (OR: 18.07; 95% CI, 2.270-143.892). Chauhan et al. [10] found that, compared to twin gestations with two normal fetuses, the presence of an anomalous co-twin significantly increased the risk of preterm birth at <32 weeks of gestation (OR:1.85; 95% CI, 1.65–2.07). Other studies further indicated an increased risk of [12] birthweight <1500 g (OR: 1.88; 95% CI 1.67– 2.12), [13] smallness for gestational age (OR: 1.21; 95% CI, 1.07–1.36), fetal death (OR: 3.75; 95% CI, 2.61–5.38), neonatal death (OR: 2.08; 95%CI 1.47–2.94), and infant death (OR:1.97; 95% CI,1.49 –2.61).

However, Harper et al [235] in 2013, analyzing 1,977 twin pregnancies from an American tertiary care center, found that the 66 twin pairs discordant for major anomalies were not at increased risk of preterm delivery or IUGR. Preterm delivery occurred in 42 (63.6%) discordant twins, compared to 1,271 (66.5%) normal twins (RR:1.0,; 95% CI, 0.8–1.2). When comparing de normal co-twin of the discordant pair to the presenting twin of the unaffected pair, IUGR was diagnosed in 15 (22.7%) normal co-twins, compared to 406 (21.3%) presenting twins in normal twins (RR 1.1, 95% CI 0.7–1.7).

Twin reversed arterial perfusion (TRAP) sequence is a rare complication of multiple pregnancies caused by defects in early embryogenesis [35], and is depicted in figure 14.

Figure 14 - TRAP twin (MAC)

Acardiac twin pregnancies are a severe complication of monochorionic twinning that occurred in less than 1% of the cases, where the acardiac twin lacks cardiac function but nevertheless grows during pregnancy because it is perfused by the pump twin through a set of placental arterial-arterial and venous-venous anastomoses. The pump twin supplies the acardiac recipient twin with blood, and although the pump twin is usually structurally normal, congenital anomalies have been reported in 10% of the cases [37]. In most cases of acardia, the development of tissues in superior regions of the body is disrupted severely, while inferior structures develop more normally. A common explanation for this disruption is hypoxia-ischemia due to twin reversed arterial perfusion (TRAP). In this condition, arterial-arterial and venous-venous anastomoses in the placenta permit twin-twin transfusion and reversal of blood flow in the umbilical vessels and aorta of the recipient twin. The heart is absent or severely deficient, either by secondary atrophy or possibly a more primary, though currently unknown, mechanism. As a result, cranial tissues are less likely to be perfused with oxygenated blood than caudal tissues. A host of cranium-cerebral anomalies are observed in acardia, including total absence of the head and brain, rudimentary brain, anencephaly, holoprosencephaly, neuronal migration defects, and near-normal brain.

Conjoined twins are MC twins joined by part of their anatomy and usually sharing one or more organs [250] (Figure 15). This is estimated to occur once every 50,000 to 200,000 births, approximately half of which are stillborn. The overall survival rate for conjoined twins is approximately 25% [226,227] with female MC twins having a higher survival rate than males (3:1). There are several types of conjoined twins and their classification is based on the location of the connection between the bodies [228,229]. Spencer et al [228] divided conjoined twins into three major groups:

1. Twins with a ventral union, including: cephalopagus (head): thoracopagus (connected at the upper portion of the thorax often sharing the heart) and representing 18% of all conjoined cases; omphalopagus (connected at the abdomen or the lower chest often sharing liver tissue) and representing 10% of all cases, and ischiopagus (connected by the hip).

2. Twins with a dorsal union, including: craniopagus (cranium) representing 6% of the conjoined cases, pygopagus (sacrum) and rachipagus (spine).

3. Twins with a lateral union, including parapagus (side twins).

Thoraco-omphalopagus (fused from the upper to the lower chest, usually sharing the heart and some parts of the digestive system) represent 28% of the cases and are the most common [230].

Figure 15 - Conjoined twins (United Kingdom)

Fetus-in-fetu (Figure 16) is a rare finding of evidence of an abnormally developed fetus in an aberrant location within the body of another individual. The pathogenesis of this anomaly is controversial, with some authors proposing that these masses are examples of well-differentiated teratomas [36].

Figure 16 - Fetus-in-fetu (India)

B. Discordant twin growth

Discordant twin growth (the difference in the weights of the fetuses) is a unique problem of the multiple gestations and an independent risk factor for adverse perinatal outcome [25, 26]. According to the American College of Obstetricians and

Gynecologists (ACOG) practice bulletin on multiple gestation [27], discordant growth is associated with increased likelihood of anomalies, intrauterine growth restriction (IUGR), preterm birth, infection of one fetus, stillbirth, umbilical arterial pH <7.10, admission to neonatal intensive care unit, respiratory distress, and death within one week of birth.

Discordance is defined by using the larger twin as the standard of growth, and can be calculated using the formula: (larger estimated or actual weight – smaller estimated or actual weight)/larger estimate or actual weight). While acknowledging the lack of consensus on the precise threshold of discordance that is linked with complications, ACOG considers a 15-25% difference in actual weight among twins to be discordant. Approximately 16% of twin gestations have discordance of at least 20% and discordance of>30% occurs in 5% of twin pairs [28].

Several known factors can influence the likelihood of twins being discordant, which should be categorized as maternal, fetal, or placental. There is a disagreement on whether maternal age, parity, or the uses of ART are risk factors for discordant growth. Maternal problems, environmental and genetic cofactors can affect fetuses in a different way and predispose to a different pattern of growth [29]. Fetal risk factors include monochorionicity, genetic potential of each fetus, structural and chromosomal anomalies and different sex. Transplacental viral infection such cytomegalovirus infection could only affect one fetus of a twin pair. Velamentous cord insertion, low placental weight or unequal placental area (different percentage of placental mass allocated to each twin) are also risk factors to discordant growth in twins.

According to Miller et al. [28] it is possible to detect discordance by sonographic examination in the first trimester through measurements of crown-rump length (CRL), with discrepancy being identified by the difference in CRL between twin pairs divided by the CRL of the larger twin. Sonographic examination can also be used in the second and third trimesters through a comparison of abdominal circumference (AC) or estimated fetal weight (EFW). When the difference among the twins' birthweight is 15-25% there is an increased risk of morbidity and death [27].

We performed an evaluation of 934 twin pregnancies [151] in which we found that 9.2% were size-discordant twin pairs (≥25%)-Study group; we compared their outcome with a group with a size discordant less than 15% (72.8% of the all database). There were no differences noted among both groups with respect to maternal age, ART, BMI, parity and chorionicity. The incidence of maternal complications was also similar among groups except for severe preeclampsia, which had higher incidence in the study group (6.4% versus 3.3% p=0.126, OR: 1.9). The rates of preterm delivery before 34 weeks and of elective CS were significantly higher in the study group (35.8% versus 12.9% and 73.3% versus 47.1% respectively). Indications for elective CS in those patients included mostly severe IUGR with signs of fetal distress (58.5%) and malpresentation (20%). CS rate in labor was similar for the groups. The study group, as expected, had a lower mean birth weight and a significantly higher incidence of SGA (68% versus 8%, p<0.001). Apgar scores adjusted for gestational age were lower in the study group and these newborn needed longer hospital stay. The study group had also a higher neonatal mortality rate (1.25% versus 0.18%, p=0.19, OR: 6.5). We concluded that discordant growth ≥ 25% adds adverse obstetric and perinatal outcome and challenges clinicians to balance the risks from fetal restriction, extreme prematurity and mode of delivery.

C. Twin-twin transfusion Syndrome (TTTS)

Twin-twin transfusion Syndrome (TTTS) is a severe complication that affects about 10 to 15% of monochorionic pregnancies [54]. TTTS appears when a circulatory imbalance results from unidirectional and uncompensated blood flow from one twin – "the donor" – to the other twin – "the recipient" [43]. According to Quintero et al. [38], TTTS is defined sonographically as the combined presence of polyhydramnios (maximum vertical pocket of amniotic fluid greater than 8 cm) in one sac and oligohydramnios (maximum vertical pocket less than 2cm) in the other sac. When the donor twin becomes severely hypovolemic and develops oligo-anuria, it will appear to be almost shrink-wrapped and 'stuck' up against the wall of the womb. This extreme sonographic sign is referred as the "stuck twin" [39]. Quintero et al. [38] introduced a staging system with prognostic value, describing the pathophysiological development of TTTS:

Stage I: The bladder of the donor twin is still visible

Stage II: The bladder of the donor twin is no longer visible (in >60 min of observation); this fetus is in renal failure.

Stage III: Critically abnormal Doppler studies characterized by absent or reverse end-diastolic velocity in the umbilical artery, pulsatile umbilical venous flow, or reverse flow in the *ductus venosus* in either twin.

Stage IV: Hydrops of one or both fetuses

Stage V: Demise of one or both fetuses

The exact pathophysiology of TTTS remains largely undetermined; it is certainly multifactorial and more complex than is currently recognized [41]. Multiple factors seem to contribute to the hemodynamic imbalance in TTTS caused by different patterns of vascular anastomosis and endocrine dysregulation:

1. Velamentous and marginal cord insertions are significantly higher in TTTS placentas [41].
2. Higher prevalence of magistral (the same diameter of the vessels starting at the cord insertion) or mixed magistral / dispersal (decreasing in diameter, starting at the cord insertion) vascular distribution patterns in TTTS placentas [41].
3. The vascular anastomoses in the placenta can be: deep with high resistance and unidirectional flow – arterio-venous anastomoses (A-V) and veno-arterial anastomoses (V-A) – or superficial with a very low resistance and bidirectional flow – arterio-arterial anastomoses (A-A) or veno-venous anastomoses (V-V). A-A anastomoses are more common in placentas without TTTS than in TTTS placentas [41], but it is possible that they must be interpreted as markers, rather than functional determinants.
4. Transfers of endocrine factors seem to be also implicated in the pathophysiology of the syndrome. Atrial natriuretic peptide and brain natriuretic peptide levels are elevated in the recipient ' s blood

and amniotic fluid [44], but seem to be correlated only with the amount of amniotic fluid and not with the severity of cardiac dysfunction [44]. Endothelin-1 levels are increased two-to-three-fold in recipients, especially in those with hydrops [45]. The recipient's reninangiotensin system is suppressed, but high levels of renin and angiotensin occur by transfer from the donor and increased placental production [46]. In the donor, renal hypoperfusion leads to oliguria and consequently to oligohydramnios, eventually resulting in renal tubular dysplasia and atrophy. The fetal reninangiotensin system is hyper activated and contributes to increased arterial resistance in the donor ' s placental territory, thereby impairing placental function and contributing to the donor's intrauterine growth restriction and decreased arterial diastolic umbilical flow. Other vasoactive mediators have been implicated in TTTS such as endothelial nitric oxide synthase, which is upregulated in the placental territory of both donors and recipients and vascular endothelial growth factor and vascular endothelial growth factor receptor-3, which are upregulated only in the recipient's placental territory [47]. Other mechanisms may be implied in the pathophysiology of TTTS such as loss of protein, compression of vessels, *in utero* placental insufficiency and differential production of growth factors [40].

TTTS remains one of the most lethal perinatal complications, with a mortality rate of 80 – 100 % and a 15 – 50 % risk of disability in survivors without treatment [42]. The optimal treatment for TTTS is selective laser photocoagulation of communicating vessels, which has led to improved single and dual twin survival [48]. Rossi et al.[49], in a systematic review and meta-analysis of neurodevelopmental outcomes after laser therapy for TTTS published in 2011, found that, overall, the prevalence of neurologic morbidity, defined as cerebral injury on imaging, cerebral palsy, blindness, and/or deafness, was 6.1%. Studies with particular emphasis on neonatal cerebral imaging have shown rates of severe cerebral lesions of 5-14% [50]. The 2011 meta-analysis also showed that the prevalence of long-term neurodevelopmental impairment was 11.1%, with rates of cerebral palsy in the range of 4-6% [51].

Vanderbilt et al. [52], in a paper published in 2012, found that for 262 consecutive laser-treated twin-twin transfusion syndrome patients, 242 (92%) had at least one neonatal survival and 185 (71%) had two survivors at 30 days. Among the entire cohort of 427 individual survivors, 46 (10.8%) had a documented cerebral lesion and 18 neonates had severe lesions (4.2%). Among the 242 "high-risk survivors", defined as those delivered at a gestational age <32 weeks, and those delivered later for whom cerebral imaging was performed because of a clinical indication, the rates for any cerebral lesion and severe cerebral lesion were 19% and 7.4% respectively. Delivery <32 weeks (OR: 4.95; *P*<0.001) and <28 weeks gestation (OR: 6.25; *P* <0.001) were associated with increased likelihood of any cerebral lesion, as depicted in Figure 17. For the cerebral lesion outcomes, "any lesions" were defined as: intraventricular hemorrhage (IVH), cystic periventricular leukomalacia, ventriculomegaly and/or hydrocephalus, microcephaly, single or multiple infarctions, congenital anomalies, porencephalic or Dandy-Walker cysts, nonspecific echogenicity, and bilateral/multiple subependymal, pseudo, or choroid plexus cysts identified on neonatal imaging. "Severe lesions" excluded cases with only grade I-II IVH and/or nonspecific echogenicity.

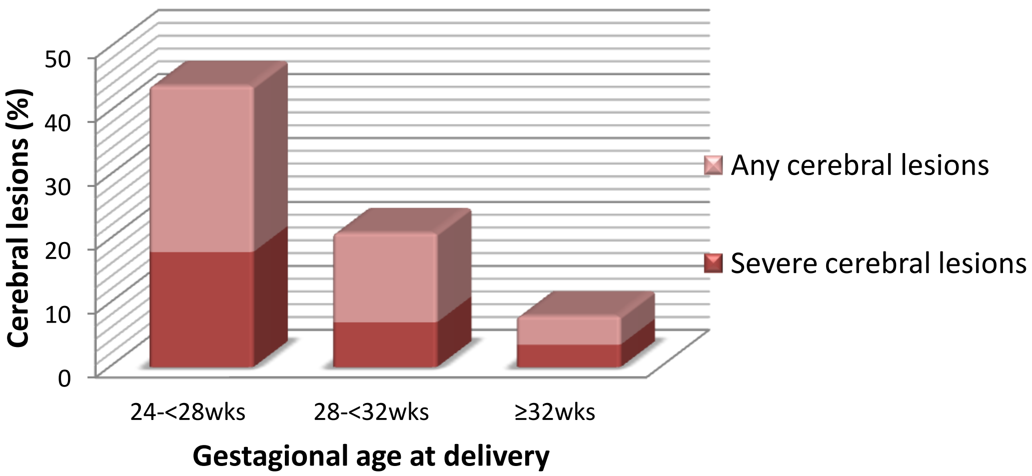


Figure 17 - Survivor cerebral lesion prevalence by gestational age.

Adapted from: Vanderbilt et al. [52] *Prevalence and risk factors of cerebral lesions in neonates after laser surgery for twin-twin transfusion syndrome.* Am. J .Obstet Gynecol 2012;207:320.e1-6.

Analyzing our database of 479 MC twins, we found 44 (9.2%) cases of TTTS for which the pregnancy progressed to 20 or more weeks. In 19 cases (43.2%) the TTTS syndrome was treated with laser photocoagulation. Premature delivery was a major complication with 15 (34%) of the cases being delivered before 28 weeks of gestation and 14 (32%) between 29 and 32 weeks. The average birth weight was only 1354±625g. There were a total of 16 intra-uterine fetal deaths and 8 cases of neonatal death (<28 days of life). We also observed 18 cases with an Apgar score less than 7 at five minutes.

Displaying our database of MC twins in a graphic form with respect to gestational age at delivery, and considering 4 groups:

- MC with maternal problems – hypertension, diabetes or thrombophilia (n=122)
- MC with fetal problems – fetal discordance >25% or abnormal Doppler or major fetal malformation or IUGR (n=100)
- MC uncomplicated (n=180)
- MC twins with TTTS (n=44)

We found that MC twins with TTTS had a higher risk of lower gestational age at delivery compared with the other groups (Figure 18).

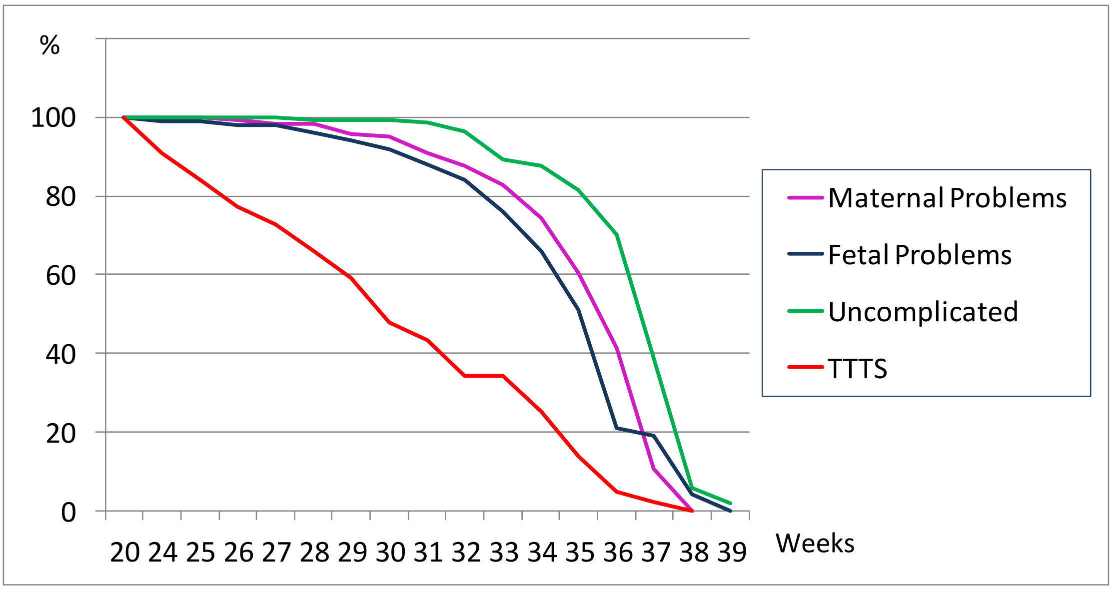


Figure 18 - MC twins gestational age at delivery according to complications during pregnancy (MAC)

Ischemic limb injury

According to Schrey et al. [53], antenatal ischemic limb injury is a rare complication of TTTS, depicted in Figure 19. The incidence of vascular limb occlusion is reported at 0.52% (4/755) for MC twins in general and 0.51% (2/391) for those cases that are complicated by TTTS [53]. Vascular limb defects appear to be at least 10-fold more frequent in MC twins than in the general population, where a prevalence of 0.02% has been reported [55].

In a retrospective, multicenter study conducted in 10 perinatal centers in Germany, USA, Jordan, Argentina, Israel and Canada, Schrey [53] identified twenty cases of limb reduction, noticed either antenatally (on ultrasound scanning or fetoscopy) or at birth. The mean gestational age at the time of diagnosis of TTTS was 21.8±2.41 weeks (16-26 weeks). No mother had a history of thrombophilia or any thromboembolic event. In 95% of the cases (19/20), the limb defect occurred in the recipient twin; in 85% of cases the defect occurred in the lower limb (17/20), of which 71% of the defects (13/17) were on the right.

The extent of the defect seemed to be correlated with TTTS severity; most of the cases with severe lower limb defects occurred in stages III or IV of TTTS (7/9; 78%), the incidence of stage III or IV TTTS was low in cases with less extensive defects (3/8; 37%). All three lesions noticed in the upper limb were limited to the hand, two of which were unilateral (stage II), the remaining one being bilateral (stage V). Various pathologic mechanisms have been suggested, namely: polycythemia-hyperviscosity syndrome [53, 55], elevated angiotensin level [55], release of thrombi after co-twin death [56], umbilical arterial-steal syndrome [57], vascular injury [58] and laser induced thrombi [59]. However, the exact pathophysiologic mechanism remains to be unknown.

Figure 19 - Laser therapy at 20 wks because of TTTS stage IV. Right lower limb injury occurred in a recipient twin first noted on US at 28 weeks'gestation.

Adapted from: Schrey et al.[53] *Vascular limb occlusion in twin-twin transfusion syndrome (TTTS): case series and literature review.* Am J Obstet Gynecol 2012; 207: 131.e1-10.

Twin anemia-polycythemia sequence (TAPS)

A variant of TTTS is the twin anemia-polycythemia sequence (TAPS), which is characterized by severe anemia in one twin and polycythemia in the other, with or without the characteristically associated oligo-polyhydramnios sequence [40]. TAPS may occur after laser surgery for TTTS – post-laser surgery form – in up to 13% of cases [70]. In these post–laser surgery TAPS cases, it is usually the former recipient who becomes anemic, whereas the former donor becomes polycythemic [70, 71]. TAPS may also occur in approximately 3-5% of "uncomplicated" monochorionic twin pregnancies – spontaneous form [72, 73].

According to Lopriore et al. [74, 75], TAPS have a similar anatomic substrate as TTTS, based on the presence of only few minuscule arterio-venous placental vascular anastomoses in the absence of superficial arterio-arterial anastomoses, leading to a slow, chronic inter-twin blood transfusion that allows more time for hemodynamic compensatory mechanisms and may prevent dysregulation of hormonal systems and the development of TTTS [74]. TAPS may occur as a complication following incomplete coagulation after TTTS treatment in around 2-6% of cases [70].

TAPS can be diagnosed antenatally with predefined Doppler-ultrasound criteria [70,247], (Middle cerebral artery peak systolic velocity > 1.5 MoM in the donor and <0.8 MOM in the recipient) or postnatally with hematologic criteria (intertwin hemoglobin difference >8.0 g/dl and intertwine reticulocyte count ratio donor/recipient >1.7) in combination with placental injection studies [72]. Postnatal diagnosis of TAPS is based on the presence of chronic anemia (with highly increased reticulocyte count) in the donor and polycythemia in the recipient, in association with typical placental angioarchitecture after injection with colored dye [72].

Lopriore et al. [75], analyzing a cohort of 19 consecutive monochorionic twins with TAPS with double survivors, compared with 38 control monochorionic twin pairs, unaffected by TAPS or TTTS, with double survivors and who were matched for gestational age at birth, found that the incidence of neonatal death and severe neonatal morbidity was similar in the TAPS group and the control group – 3% (1/38) vs. 1% (1/76), and 24% (9/38) vs. 28% (21/76), respectively. Severe cerebral injury was detected in 1 infant (5%) in the TAPS group and 1 infant (2%) in the control group. They concluded that neonatal mortality and morbidity rates in a select population of TAPS neonates were similar to control neonatal rates; with neonates with TAPS showing mainly short-term hematologic complications that require blood transfusions at birth (for the anemic donor) or partial exchange transfusions (for the polycythemic recipient), but with no effects in other organ systems. They speculated that the low rate of neonatal morbidities in TAPS may be related to a milder form of hemodynamic alteration during fetal life, in contrast with TTTS.

D. The Vanishing twin syndrome

Pregnant loss is another problem of twin pregnancy. The vanishing twin syndrome (figure20) is defined as a first-trimester missed abortion of one of the twins [94]. This phenomenon has been reported since the early days of ultrasound. Hellman et al. [93] reported the earliest sonographic demonstration of the vanishing twin in 1973, but with the advent of transvaginal ultrasound, many others report have demonstrated more clearly the disappearance of one of the sacs. The frequency of singletons originating from a twin gestation ranges from 10.4% to 12.2% [94, 95]. Spontaneous reduction of one or more gestational sacs occurring before the 12th gestational week has been described in 36% of twin pregnancies [96]. Vaginal bleeding may be the only sign in a high percentage of women experiencing this phenomenon.

Figure 20 - Ultrasound of a vanishing twin pregnancy

Mansour et al. [97] found, in a cohort of ICSI pregnancies, that the incidence of pregnancies associated with vanishing fetuses was 9% (264 out of 2,829) and that the miscarriage rate in the singleton pregnancies after vanishing fetuses (5%) was statistically significantly lower than in the singleton pregnancies from the start (20%) and even in the twin pregnancies, the miscarriage rate was statistically significantly lower in the group associated with a third vanishing fetuses (2% vs. 11%, p=0.02). They also found that the live-birth rate and the take-home baby rate per pregnant woman were statistically significantly higher in the singleton pregnancies after vanishing fetuses as compared with singleton pregnancies from the start (92% vs.76%, and 90% vs. 75%, respectively), evidenced in Table 8.

Table 8 - Pregnancy outcome in singleton and twin pregnancies with vanishing fetuses.

Adapted from: Mansour et al.[97] *The impact of vanishing fetuses on the outcome of ICSI pregnancies.* Fertil Steril 2010; 94:2430-2432

	Singleton after vanishing fetuses	**Singletons from the start**	**Twins after vanishing fetuses**	**Twins from the start**	**P value (for all groups)**
Nº of pregnant women	**206**	**1,764**	**58**	**616**	
Nº of miscarriage, rate(%)	**10(5%)**	**352(20%)**	**1(2%)**	**70(11%)**	**<0.001**
Gestational age at delivery (wks)±SD	**36.8±3.3**	**37±3.3**	**34.3±4.2**	**35.2±3.6**	**<0.001**
Live-birth rate/pregnant women (%)	**190/206(92%)**	**1,346/1,764(76%)**	**55/58(95%)**	**515/616(84%)**	**<0.001**
Take-home-baby rate/pregnant women (%)	**186/206(90%)**	**1,320/1,764(75%)**	**51/58(88%)**	**490/616(80%)**	**<0.02**
Nº of live babies up to 1 month after delivery	**186**	**1,320**	**96**	**947**	

According to Matias et al. [98] a significant advantage of twins over singletons in terms of early loss rates of the entire pregnancy seems apparent in all of the published data [98], Figure 21.

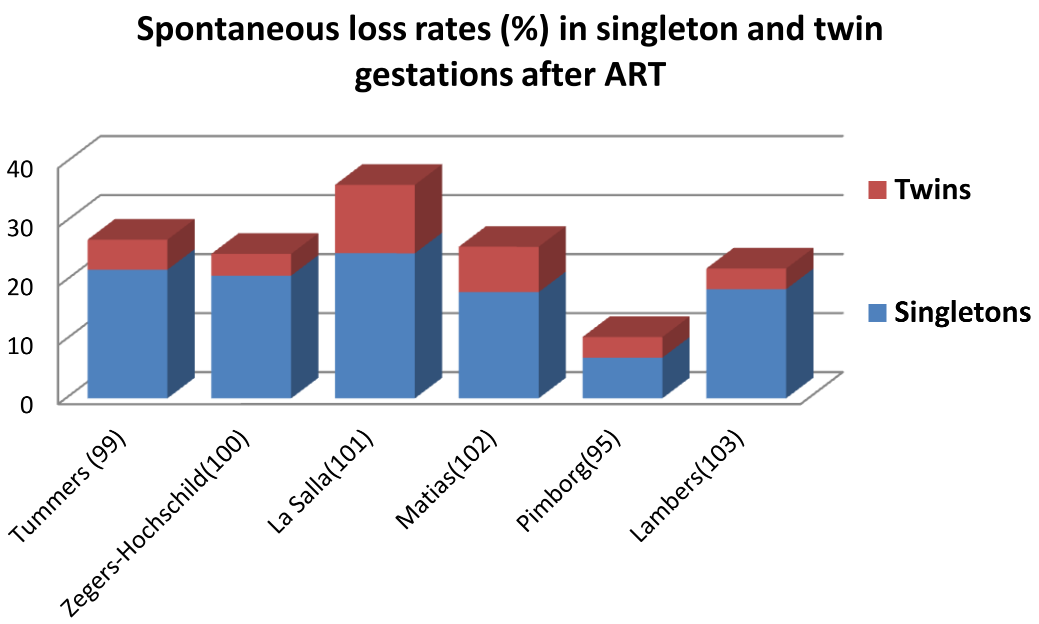


Figure 21 - Spontaneous loss rates after ART.

Adapted from: Matias et al.[98] *Early loss rates of entire pregnancies after assisted reproduction are lower in twin than in singleton pregnancies* Fertil Steril 2007;88:1452–1454.

However, Shebl et al. [104], comparing 46 singletons originating from a twin gestation with 92 singletons from a single gestation, found a higher risk for survivors of the vanishing twin syndrome with respect to pregnancy complications. The survivors' cohort showed a lower birth weight than the control group (2876.3 ± 600.5 g vs. 3249.6 ± 624.5 g), a higher frequency of low birth weight (26.1% vs. 12.0%) and smallness for gestational age (32.6% vs. 16.3%). They concluded that such pregnancies needed to be carefully monitored.

Pinborg el al. [95,105] reported the same results. Analyzing IVF singletons with a spontaneous fetal loss, they found a significantly higher rate of small for gestational age (OR: 1.50, 95% CI 1.03–2.20) and term low birth weight compared with singletons from a single embryo (OR: 1.71, 95% CI 1.06–2.74).

Luke et al. [106] suggested that fetal reduction in the first trimester, whether induced or spontaneous, may cause chronic inflammation and subsequent adversely affect placentation, leading to inadequate development or abnormal localization of the placenta. That may slow growth for the remaining fetuses resulting in IUGR and preterm birth.

We evaluated a small cohort of singletons originating from DC twins (n=19) and compared their outcomes with a control group of 955 DC twins. No statistically significant differences were found between both groups with respect to maternal age, nulliparity and spontaneous pregnancies, as shown in Table 9.

Table 9 - Vanishing twin versus DC twins (MAC-2012)

	Vanishing twins N=19	**DC twins N=955**	**p-Value**
Maternal age (years)	31.1±6	30.7±5	0.84
Nulliparity (%)	57.8%	57.4%	0.96
Spontaneous pregnancies (%)	68.4%	68.6%	0.99

However, with respect to pregnancy complications, we did find similar rates for the vanishing group compared to the DC group, Figure 22. Despite the fewer numbers analyzed (n=19), we agree with Shebl et al. [104] that such pregnancies need to be carefully monitored, as they seem to have similar rates of maternal complications than DC twins.

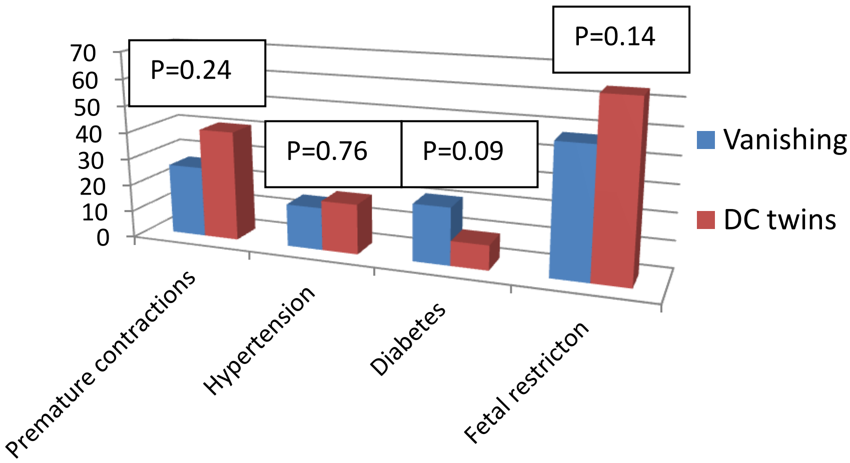


Figure 22 - Maternal problems, Vanishing twins versus DC twins (MAC-2012)

E. Neurological morbidity in twin neonates

Twins are associated with a variety of adverse outcomes, including **delayed development, impaired sensorimotor function**, and **cerebral palsy** [76]. Topp et al. [18] found that, moreover, 5 to 10% of all cerebral palsy cases occur in twins, which represents more than 4 times the observed frequency in the general population.

O'Callaghan et al. [77], studying a cohort of 587 individuals with cerebral palsy and 1,154 with non-cerebral palsy controls, found that multiple birth (OR: 6.62, 95% CI 4.00–10.95) was one of the most important risk factors associated with cerebral palsy, alongside preterm birth, intrauterine growth restriction and perinatal infection.

Adegbite et al. [78] determined the incidence of neurologic morbidity in preterm monochorionic (MC) and dichorionic (DC) twins. To achieve this, they collected the perinatal, neonatal, and infant follow-up data of 76 MC and 78 DC twins born between 24 and 34 weeks of gestation, for a total of 295 infants. They evaluated the risks of neuromorbidity in the surviving infants in relation to chorionicity, discordant birth weight (>20%), twin-twin transfusion syndrome (TTTS), and cotwin death.

MC infants had a higher incidence of cerebral palsy (8% vs. 1%, $p < 0.05$) and neurologic morbidity (15% vs. 3%, $p < 0.05$) than DC infants. The risk of impaired neurodevelopment was also higher in MC infants with discordant birth weight (42%, $p< 0.01$), TTTS (37%, $p < 0.01$), and cotwin death (60%, $p< 0.01$) compared with those with concordant birth weight (8%). In MC pregnancies, the cerebral palsy risk was higher in infants with discordant birth weight than those with chronic TTTS (19% vs. 4%, $p < 0.05$). However, discordant DC infants also had higher neuromorbidity compared with the concordant group (5% vs. 1%, $p< 0.05$). In both MC and DC discordant infants, neurologic morbidity was independent of growth restriction. They concluded that neurologic morbidity in the preterm MC infants was 7-fold higher than in DC infants because of chronic TTTS, discordant birth weight, and cotwin death in uterus.

Pharoah et al. [79], analyzing the reply cards of the parent participants of a survey including parents of 572 surviving children of a co-twin fetal or infant death and parents of 9,380 twin pairs in which both twins survived infancy, found that when the co-twin suffered a fetal or infant death, the like-sex survivor was at significantly greater risk of cerebral palsy than an unlike-sex twin, relative risk 2.55 (95% CI 1.23 to 5.27; $p = 0.01$). Among the generality of twins, like-sex compared with unlike-sex twins were at greater risk of cerebral palsy particularly if one twin suffers a fetal or infant death.

Livinec et al [80] analyzed the data from 1,954 children for whom a medical questionnaire was completed at the age of 2 years and representing 83% of the surviving children resulting from all very preterm children (< 33 weeks) born in 1997 in 9 regions of France. They found that the proportion of cerebral palsy was 8% in singletons and 9% in twins. For singletons, spontaneous preterm labor, preterm premature rupture of membranes (PPROM) with short latency, and prolonged PPROM were associated with a higher risk of cerebral palsy than was hypertension, but in twins no significant association was found between these pregnancy complications and the risk of cerebral palsy.

5. Timing and mode of delivery

Twins have a higher risk of fetal demise throughout the pregnancy and the optimal gestational period may be shorter for twins than for singletons [107,108,109].

Minakami et al. [110] suggested, in 1996, that the estimated date of delivery for multifetal pregnancies be set at 37 to 38 weeks gestation, rather than the usual 40 weeks gestation. Their study of singleton and multiple birth infants in Japan between 1989 and 1993 showed that fetal and early neonatal death rates for fetuses and infants of multifetal pregnancies were lowest at 38 and 37 weeks gestation, respectively.

Kiely et al. [111], analyzing a USA cohort (1989-1991), showed that the perinatal mortality rates were lowest at 40 weeks gestation for singletons and at 38 weeks gestation for twins.

In 2001, Hartley et al. [112] published the result of a population-based retrospective study including 9,740 twin pairs born in Washington State during 1987 through 1997, which sought to determine the gestational age at delivery for twins that was associated with the lowest perinatal mortality rate, the lowest incidence of respiratory distress syndrome (RDS), and the lowest rates of long (≥5 days) hospital stays. They used twin pairs rather than individual twins as the units of analysis, because they believed that the assessment of twin pregnancy outcomes must account for the health of both infants. They found that 526 of 9,744 twin pairs were affected by at least one perinatal loss, resulting in a pair rate of 54 losses (single or double) per 1,000 pairs.

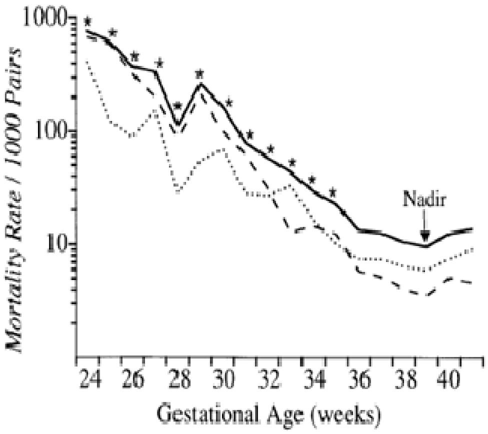
Dividing twin pairs into two categories, those with non-discordant birth weight and without any malformations (n = 6,054) and those with either discordant birth weight, malformations or both (n = 1,053), revealed that the lowest point of perinatal mortality rate was 39 weeks of gestation in the non-discordant group (1.5 losses/1,000 pairs) and 38 weeks gestation in the second group (48.0 losses/1,000). The leading four causes of death for twin fetuses and infants overall were:

- complications of the placenta, cord, and membranes;
- congenital anomalies;
- short gestation unspecified low birth weight (LBW),
- RDS.

Fourteen percent of twin deaths occurred in pairs born at ≥36 weeks of gestation; less than a third of these deaths were attributed to congenital anomalies. Among the pairs born at ≥36 weeks of gestation, the mortality rate of the second twin was about 60% greater than the observed in the first twin.

Analyzing only the 3,176 twin pairs delivered vaginally after spontaneous labor, they found that the lowest perinatal mortality rate (5.6 losses/1,000 pairs) occurred at 37 weeks of gestation. Perinatal mortality rates were 10.5 losses/1,000 pairs and 15.2

losses/1,000 pairs for twins with spontaneous vaginal deliveries at 36 and 38 weeks of gestation, respectively, as shown in Figure 23.



Perinatal death rate – solid line

Pair fetal death – dotted line

Neonatal death rate – dashed line

*Week with perinatal mortality rate significantly different from *Nadir*

According to gestational age at delivery

Figure 23 - Perinatal death rate, pair fetal death and neonatal death rate.

Adaped from: Hartley et al.[112]. *Perinatal mortality and neonatal morbidity rates among twin pairs at different gestational ages: Optimal delivery timing at 37 to 38 weeks' gestation.* Am J Obstet Gynecol 2001;184:451-458

The incidence of RDS was >100 cases (single or double) per 1,000 pairs for twins delivered at <33 weeks of gestation and it dropped sharply for those delivered between 33 and 36 weeks of gestation, as depicted in Figure 24.

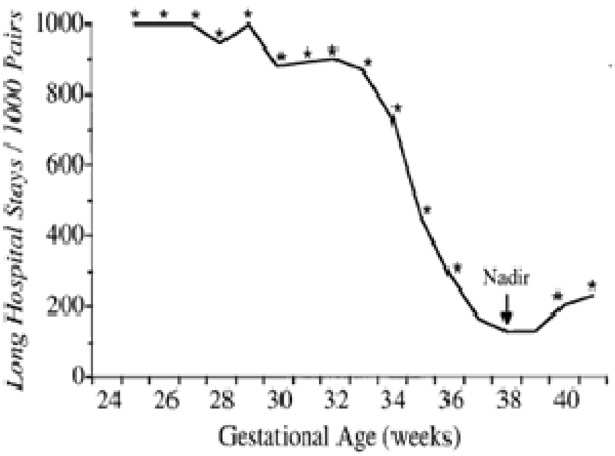
Pair RDS incidence according to gestational age at delivery among twin pairs in which both infants survived ≥ 28 days

*****Week with RDS rate significantly different from *Nadir*

Figure 24 - Pair RDS incidence according to gestational age at delivery.

Adaped from: Hartley et al. [112] *Perinatal mortality and neonatal morbidity rates among twin pairs at different gestational ages: Optimal delivery timing at 37 to 38 weeks' gestation.* Am J Obstet Gynecol 2001; 184:451-458

Rates of long hospital stays of 127.1 cases (single or double) per 1,000 pairs reached a minimum for twins born at 38 weeks of gestation, as seen in Figure 25.



*Week with long hospital stay rate significantly different from *Nadir*.

Figure 25 - Pair rates of long (≥5 days) hospital stays according to gestational age at delivery among twin pairs with hospital stay that were discharged home.

Adaped from Hartley et al. [112] *Perinatal mortality and neonatal morbidity rates among twin pairs at different gestational ages: Optimal delivery timing at 37 to 38 weeks' gestation*. Am J Obstet Gynecol 2001; 184:451-458

Hartley et al. [112], investigating the optimal gestational age for twin delivery with twin pairs as the units of analysis, suggested that the optimal gestational age for twin delivery was 37 to 38 weeks of gestation. They justify this opinion by noting that:

- the rates of perinatal mortality, RDS, and long hospital stay were only slightly lower for twin pairs born at 38 weeks of gestation compared with those born at 37 weeks of gestation,
- the rates at 39 weeks of gestation did not show further improvements relative to the rates at 38 weeks of gestation,

Considering that the loss of one twin is devastating for the family and that the best outcome for a twin pregnancy is the delivery of 2 healthy infants, and noting that term twin pairs (≥36 weeks of gestation) face >5 times the risk of perinatal loss seen among singletons, they conclude that induction of labor at 37 to 38 weeks of gestation should be routinely considered in twin pregnancies.

Dodd et al. [231] in a Cochrane Systematic Review reported that a policy of elective delivery from 37 weeks' gestation compared with expectant approach for women with an otherwise uncomplicated twin pregnancy was associated with improved infant outcome.

Again, Hartley et al. [113], in 2010, analyzing a cohort of 21,569 twin pairs born alive at 24–42 weeks of gestation between 1980 and 2005 in Washington State, and considering twin pair gestational age at delivery as very preterm (24–31 weeks), later preterm (32–36 weeks), and term (37–42 weeks), found that the gestational age distribution curve showed a steady increase in twin pair preterm births from 1980 to 2005, as seen in Figure 26.

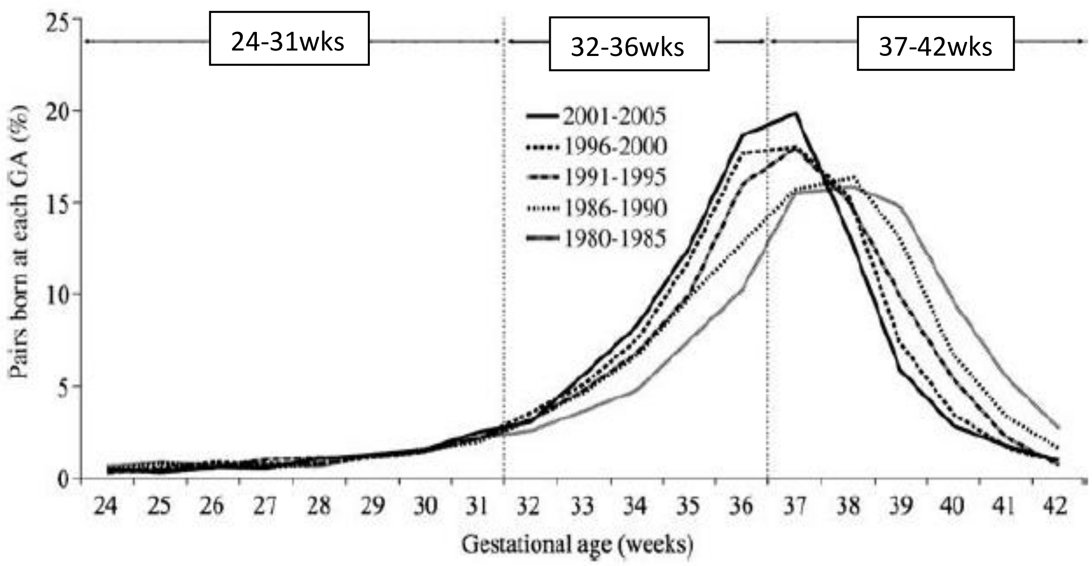


Figure 26 - Gestational age distribution curve.

Adapted from Hartley et al. [113]. *Increasing rates of preterm twin births coincide with improving twin pair survival.* J. Perinat Med 2010; 38: 297–303

Very preterm births remained stable at 8%, whereas later preterm births increased from 28% to 48% and term births decreased from 64% to 44% (p=0.0001). Analyzing the mode of delivery they found that pairs delivered by cesarean without induction increased noticeably (from 39% in 1989–1990 to 53% in 2001–2005) and had a high proportion of preterm births, while non-induced 1st twin vaginal deliveries decreased.

Labor inductions also increased in frequency but were associated with relatively few preterm births.

Using dichotomous gestational age and comparing 2001–2005 to 1980–1985, they found that the RR of preterm birth was 1.54 (95% CI 1.46–1.61). Utilizing the ''per pair-at-risk'' approach to fetal deaths, they found the risk of fetal death was highest for term pairs and that the term risk had declined from 1980–1985 to 2001–2005.

The need for respiratory support increased through time, from 11% of twin pairs in 1989–1990 to 19% in 2001–2005 (p=0.0001), but the pair rates of neonatal mortality decreased through time, from 3.4% in 1980–1985 to 1.3% in 2001–2005 (p=0.0001).

The RR of neonatal death in a pair in the later years versus at the start of the study period was 0.38 (95% CI 0.28–0.50). They concluded that the observed decline in the risk of term fetal deaths may be due to obstetric interventions to prevent post-maturity at ≥40 weeks in twins.

Ananth et al. [17], carrying out a retrospective cohort study of twin live births and stillbirths in the United States between 1989 and 1999 (n=1,102,212), found that the rates of labor induction and cesarean delivery among twin live births increased by 138% (from 5.8% to 13.8%) and 15% (from 48.3% to 55.6%) respectively, and that these changes were accompanied by a 43% decline in the stillbirth rate between 1989 and 1999 (from 24.4 to 13.9 per 1,000 fetuses at risk).

Between 1989 and 1999, having excluded newborns weighing < 500 g, the rates of labor induction among twins at 22-27 weeks, 28-33 weeks and ≥ 34 weeks of gestation increased by 95%, 131% and 127%, respectively and the CS delivery rates increased by 55%, 29% and 2% in the same gestational age categories as shown in Figure 27.

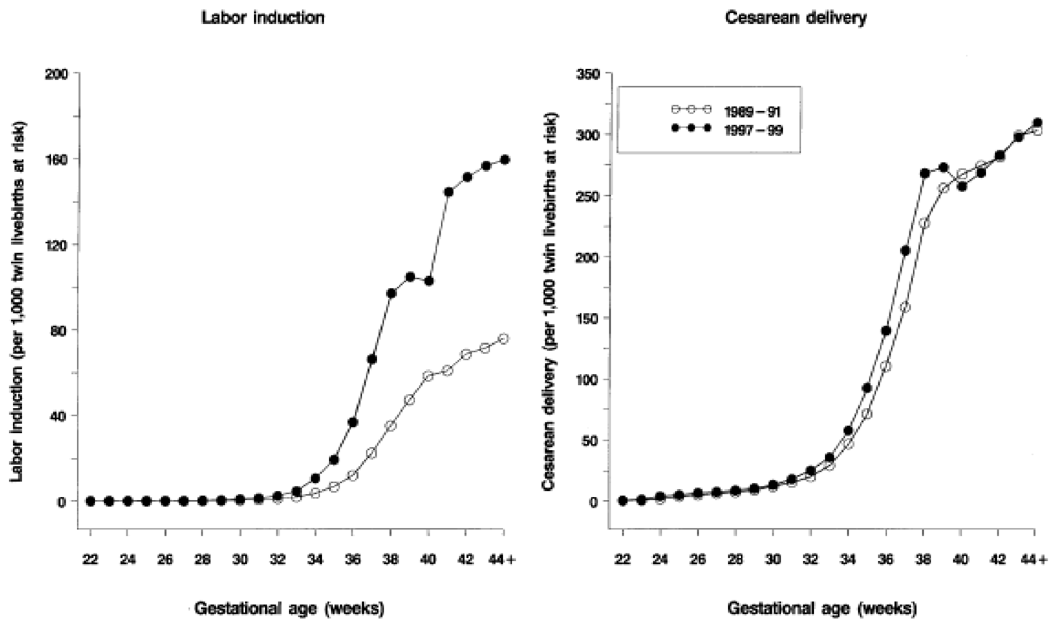


Figure 27 - Increase in the rates of CS and labor induction in twins.

Adapted from: Ananth et al. [17] Trends in twin neonatal mortality rates in the United States, 1989 through 1999: influence of birth registration and obstetric intervention. Am. J. Obstet. Gynecol. 2004; 190:1313-1321

Ananth et al. [17] found a 25% RR 0.75, 95% CI (0.72-0.79) decline in stillbirth rate between 1989-91 and 1997-99 and that the decline was larger at later gestational ages (at ≥32 and ≥34 weeks) where the largest absolute increases in labor induction rates were observed. They concluded that the use of CS delivery and, especially, labor induction for twin pregnancies has increased substantially in the USA over the last decade, and these changes have been associated with a large decline in the rate of stillbirth among twins.

Morikawa et al. [114], analyzing a cohort of 3,241 and 6,581 women with MC-DA and DC twins, respectively, who gave birth at ≥ 22 weeks of gestation, demonstrated that women with MC-DA twins were 2.2 times more likely to experience stillbirth (SB) than women with DC twins (2.5 % versus 1.2 %), Table 10. Furthermore, after a single intrauterine fetal death, the co-twin died in uterus or within 7 days of life more frequently among MC twins than among DC twins: 42.7 % (35/82) vs. 2.6 % (2/76); RR, 16.2; 95 % CI (4.0 – 65.1) .

Table 10 - Outcomes of the co-twin after single intrauterine fetal death (IUFD) according to placental chorionicity.

Adapted from: Morikawa et al. [114]. *Prospective risk of stillbirth: monochorionic diamniotic twins vs. dichorionic twins.* J.Perinat Med. 2012; 40:245–249

Co-twin outcome	MC	DC	RR(95% CI)	p-Value
Stillbirth	29(35.4%)	2(2.6%)	13.4(3.3-54.4)	<0.0001
Early Neonatal death (<7days of life)	6(7.3%)	0(0%)	12.2(1.5-101)*	0.0290
Stillbirth or Early neonatal death	35(42.7%)	2(2.6%)	16.2(4.0-65.1)	<0.0001
Alive	47(57.3%)	74(97.4%)	1.29(0.90-1.85)	<0.0001
Total	82(100%)	76(100%)		

*On the assumption that one women with DC twins experienced early neonatal death
IUFD occurred in 82 of 3241 women (2.5%) with MC twins and 76 of 6581(1.2%) women with DC twins

In this study, the prospective risk of SB abruptly increased among women with DC twins at ≥38 weeks of gestation, likely because DC twins with a twin death had delivered later, Figure 28 and 29.

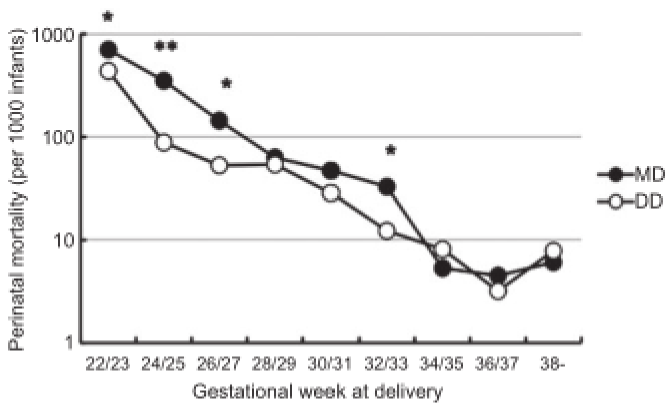


Figure 28 - Perinatal mortality rate (IUFD and early neonatal death within 7 days of life) according to gestational week at delivery (per 1000 infants). *p<0.05 and **p<0.0001 between two groups.

Adapted from Morikawa et al.[114]. Prospective risk of stillbirth: monochorionic diamniotic twins versus dichorionic twins. J.Perinat Med. 2012; 40:245–249

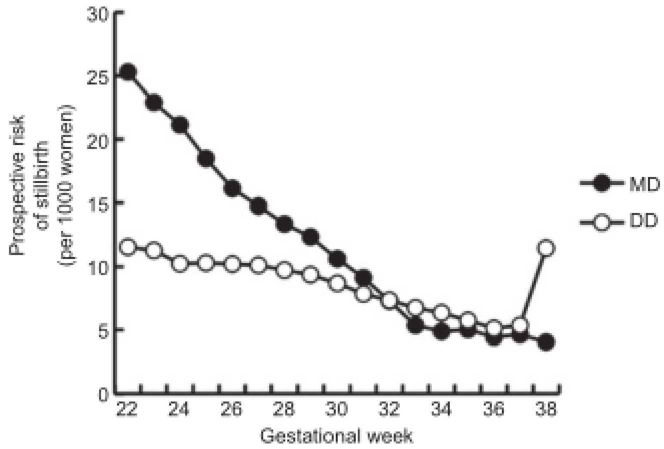


Figure 29 - Prospective risk of stillbirth among women who reached a given gestational week (per 1000 women)

Adapted from Morikawa et al.[114]. *Prospective risk of stillbirth: monochorionic diamniotic twins* versus *dichorionic twins.* J.Perinat Med. 2012; 40:245–249

In 2005, Barigye et al. [154] published a study of 151 apparently uncomplicated, intensively monitored MC-DA twin pregnancies. The term ‘‘uncomplicated’’ was used to denote pregnancies without evidence of TTTS on ultrasound that also had appropriate and concordant fetal growth, as well as normal growth velocity in each of two structurally normal twins. These pregnancies also had normal umbilical artery (end diastolic frequencies present), umbilical vein (no pulsations), and/or ductus venosus (positive a wave) Doppler waveforms in each twin.

Uncomplicated MC-DA pregnancies were monitored according to a standard protocol, which comprised routine first trimester nuchal translucency assessment and chorionicity determination, a detailed anomaly scan and fetal echocardiography at 20 weeks, and subsequently fortnightly scans for growth, amniotic fluid, and Doppler (umbilical artery, umbilical vein, and/or ductus venosus). Elective delivery was scheduled in otherwise uncomplicated pregnancies for the period between 36 and 37 weeks of gestation. They excluded pregnancies complicated by twin reversed arterial perfusion, as well as high-order multiple, monoamniotic, and conjoined pregnancies.

From this cohort of 151, there were ten unexpected fetal deaths in seven uncomplicated MC-DA pregnancies (three double deaths and four single deaths) after 24 weeks, giving an overall incidence of 4.6% per pregnancy 95%CI (1.9%–9.9%), Figure 30.

Rate and Prospective Risk of Unexpected Fetal Death in 151 Intensively Monitored, Uncomplicated MCDA Pregnancies after 24 wk of Gestation

Gestational Age (Weeks $^{+Days}$)	Number of Continuing Pregnancies	Number of Continuing Fetuses	Number of Deaths per 2-wk Block per Pregnancy	Number of Deaths per 2-wk Block per Fetus	Rate of Death per Pregnancy	Rate of Death per Fetus	Number of Deaths in Continuing Pregnancies	Number of Deaths in Continuing Fetuses	Prospective Risk of Death per Pregnancy	Prospective Risk of Death per Fetus
24^{+0}–25^{+6}	151	302	0	0	0 in 151 (0/151)	0 in 302 (0/302)	7	10	1 in 22 (7/151; 4.6%)	1 in 30 (10/302; 3.3%)
26^{+0}–27^{+6}	151	302	0	0	0 in 151 (0/151)	0 in 302 (0/302)	7	10	1 in 22 (7/151; 4.6%)	1 in 30 (10/300; 3.3%)
28^{+0}–29^{+6}	150	300	1	2	1 in 150 (1/150)	1 in 150 (2/300)	7	10	1 in 21 (7/150; 4.7%)	1 in 30 (10/300; 3.3%)
30^{+0}–31^{+6}	146	292	0	0	0 in 146 (0/146)	0 in 292 (0/292)	6	8	1 in 24 (6/146; 4.1%)	1 in 36 (8/292; 2.7%)
32^{+0}–33^{+6}	139	278	2	2	1 in 69 (2/139)	1 in 139 (2/278)	6	8	1 in 23 (6/139; 4.3%)	1 in 35 (8/278; 2.9%)
34^{+0}–35^{+6}	120	240	3	5	1 in 40 (3/120)	1 in 48 (5/240)	4	6	1 in 30 (4/120; 3.3%)	1 in 40 (6/240; 2.5%)
$\geq 36^{+0}$	93	186	1	1			1	1		
Total			7	10						

Figure 30 - Rate and prospective risk of unexpected fetal death in MCDA twins.

Adapted from: Barigye et al. [154] *High risk of unexplained late fetal death in monochorionic twins despite intensive ultrasound surveillance: a cohort study.* PloS Med. 2005; 2:e172.

Their data suggested that even intensively monitored, apparently healthy MC-DA pregnancies remain at substantial risk of IUFD after 24 weeks (4.6% of pregnancies and 3.3% of fetuses). IUFDs after 24 weeks occurred in the third trimester, and predominantly after 32 weeks of gestation, at which time the prospective risk of subsequent IUFD was 1/23 pregnancies.

The fetal deaths in their study occurred despite strategies aimed at preventing them, through fortnightly ultrasound and Doppler surveillance in a tertiary fetal medicine unit, and elective delivery at 36–37 weeks.

In the discussion they comment that the high rate of unexpected third trimester fetal death might be obviated by a range of preventative strategies:

- The increase in the frequency of monitoring. Although growth is only usefully measured every 2 weeks, more frequent surveillance could include amniotic fluid volume and distribution, and fetal Doppler waveforms;

- Earlier delivery. They claim that neurological morbidity in MC twins can be mostly attributed to a hemodynamic imbalance associated with MC placentation (79,114), and that in modern days, delivery after 32 weeks is not associated with a high risk of neurodevelopmental sequelae. They therefore reason that elective premature delivery of uncomplicated MC twins at or after 32 weeks may, in fact, reduce their risk of neurodevelopmental injury, since single IUFD in MC twins is widely regarded as a risk-factor for cerebral palsy [116,117].

Both DC and MC twins are associated with a higher risk of perinatal mortality when compared with singletons [119]. Ong et al. [120] published a review analyzing the risk for the co-twin after single IUFD and reported a risk of 12% for MC twins (95% CI 8–19) and of 4% for DC twins (95% CI 2–7%).

Hillman et al. [118] performed another systematic review and meta-analysis on the same subject, evaluating the rates of IUFD in the two kinds of twins (DC vs. MC), the rate of preterm delivery, perinatal death, abnormal cranial imaging (reported within 4 weeks after delivery) and neurologic morbidity in the surviving fetus. They included 22 articles in the systematic review and meta-analysis (6,225 pregnancies and 343 incidences of single intrauterine fetal demise), Figure 31.

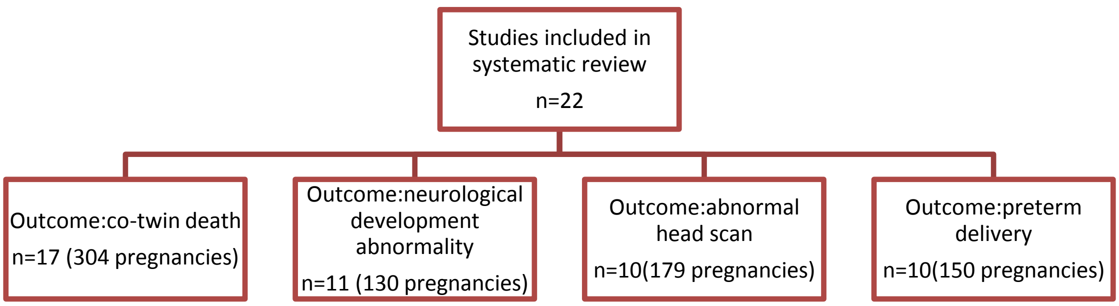


Figure 31 - Systematic review of the prognosis of the co-twin in the event of single intrauterine fetal death.

Adapted from: Hillman et al.[118]. *Co-Twin Prognosis After Single Fetal Death: A Systematic Review and Meta-Analysis* Obstet Gynecol 2011;118:928–940

Hillman et al. [118] found that single IUFD was a relatively rare event in a twin pregnancy (2-7%), and that after single IUFD MC co-twins were: at 15% (95% CI 9.1–20.9) risk for co-twin death, had a 68% (95% CI 56.7–78.5) risk of preterm delivery, 34% (95% CI 28.8–46.1) risk for abnormal postnatal cranial imaging and 26% (95% CI 16.5–34.6) risk of neurodevelopmental morbidity. The analogous values for DC twins were: 3% (95% CI 0.4–5.7) risk for co-twin death, 54% (41.5–66.9) risk of preterm delivery, 16% (95% CI 7.8–23.5) risk of abnormal postnatal cranial imaging and 2% (95% CI 1.6–4.9) risk of neurodevelopmental morbidity, Figure 32.

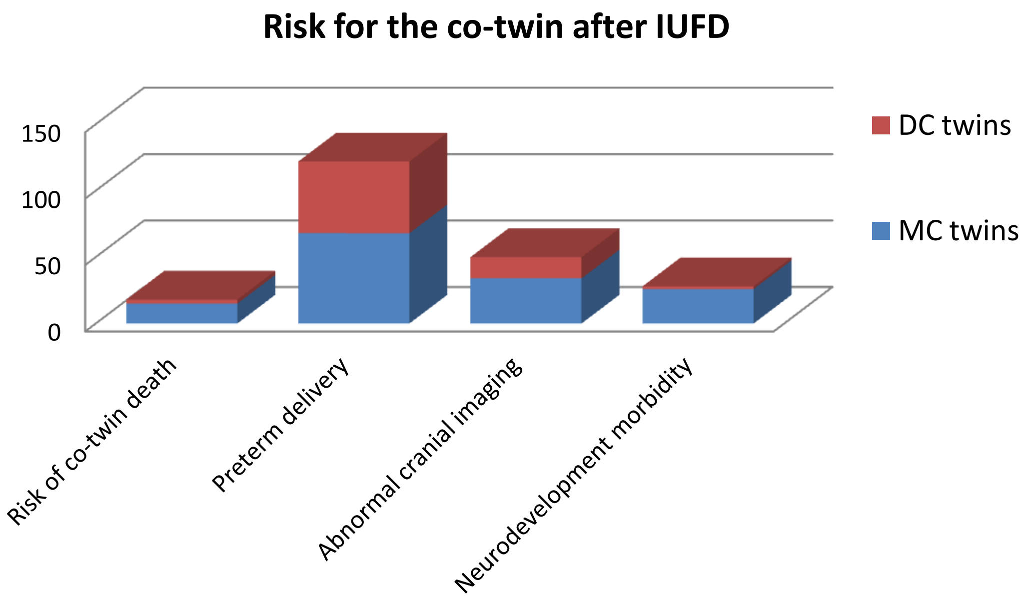


Figure 32 - Risk for the co-twin after IUFD

Adapted from: Hillman et al. [119]. *Co-Twin Prognosis After Single Fetal Death: A Systematic Review and Meta-Analysis* .Obstet Gynecol 2011; 118:928–940

The odds of MC death after single twin death in the second and third trimesters were five-times higher when compared with DC pregnancies (OR 5.24, 95% CI 1.75–15.7, $p<0.05$). They found the same results with respect to neurologic morbidity, with almost five-times larger odds (OR 4.81, 95% CI 1.39 –16.6, $P<0.05$) of a MC twin having neurologic morbidity, compared with a DC twin.

The effect of gestation and single IUD on preterm delivery rates revealed that, at 28–33 weeks of gestation, MC twins have substantially higher odds for prematurity than DC twins (OR 4.96). Neurodevelopmental morbidity did appear to also be affected by gestation of single IUFD. When it occurred between 28 and 33 weeks of gestation, MC twins had 7.57-times the chance of morbidity compared with DC twins at the same gestational age. If the demise occurs at more than 34 weeks, then the odds for MC twins appears to decrease (OR 1.48, 95% CI 0.13–17.5).

MC and DC twins are associated with an increased risk of other obstetrics complications, such as preeclampsia, gestational diabetes, fetal growth restriction, or growth discordance, as we have discussed before. Although preterm delivery is the most significant problem in twin gestation, some twin pregnancies reach 38 weeks, and are at increased risk of fetal demise without any additional benefit from further intrauterine life [17,115,121].

The Royal College of Obstetricians and Gynaecologists (RCOG), in the Setting Standards to Improve Women's Health 2001 on the subject of Induction of labor [122], reported the retrospective study of all singleton and multiple pregnancies in Japan [110] between 1989 and 1993 which demonstrated that the risk of perinatal death was increased for fetuses of multiple pregnancy compared with singletons born at 40 weeks (1.8% vs. 0.16%). The same study showed that, in multiples, the percentage of perinatal deaths was 1.1-1.2% between 37 and 39 weeks of gestation, 1.8% at 40 weeks, 2.2% at 41 weeks and 3.7% at 42 or more weeks. Other authors also reported the benefits of the obstetric intervention on the trends in stillbirths [17].

Wilmink et al. [135], using the Netherlands Perinatal Registry, analyzed 54,082 live-born neonates of twin pregnancies born from January 2000 through December 2007. They only included neonates born by an elective CS with 35 weeks or more weeks of gestation, they excluded neonates born by a planned CS registered with a maternal and/or fetal indication or born by an emergency CS.

Analyzing a cohort of n = 2,228 neonates, the absolute risks for severe adverse neonatal outcome were 8.7% between 35 and 35+6, 1.7% between 36 and 36+6, and 0.7% between 37 and 37+6 weeks, compared with 1.1% between 38 and 41+6 weeks of gestation ($p<0.0001$).

For mild neonatal morbidity the absolute risks were 22.1% between 35 and 35+6, 22.1% between 36 and 36+6, and 7.6% between 37 and 37+6 weeks, compared to 5.5% between 38 and 41+6 weeks of gestation ($p<0.0001$).

Admission to the NICU demonstrated risks of 4.8% between 35 and 35+6, 1.0% between 36 and 36+6, and 0.5% between 37 and 37+6 weeks, compared with 0.2% between 38 and 41+6 weeks of gestation ($p<0.0001$).

Admission to any neonatal ward presented risks of 60.6% between 35 and 35+6, 36.9% between 36 and 36+6, and 19.2% between 37 and 37+6 weeks, compared with 15.3% between 38 and 41+6 weeks of gestation ($p<0.0001$).

Compared to neonates born between 38 and 41+6 weeks of gestation, neonates born between 35 and 35+6 weeks were at significantly higher risk for all outcomes measures and, between 36 and 36+6 weeks, at significantly higher risk for mild neonatal morbidity and hospitalization >5 days. However there were no significantly higher risks between 37 and 37+6 weeks of gestation.

The incidence of intrauterine fetal demise between 36 and 39+6 weeks of gestation appears stable, at around 1.0 - 2.0 per 1,000 fetus. Thereafter this risk increases to 5.1 and 8.9 per 1,000 fetus at 40 and >41 weeks of gestation, respectively. They concluded that, in the absence of fetal or maternal indications, an elective CS should not be performed before 37 weeks of gestation.

Zipori et al. [133] evaluated the neonatal respiratory morbidity (NRM), namely respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN). Analyzing 711 twin pregnancies (1,422 live-born neonates) born beyond 35 weeks of gestation. They found that, among the 1,422 neonates, 74 (5.2%) experienced neonatal respiratory morbidity [RDS: 23 (1.6%) + TTN: 51 (3.6%)]. Maternal age >25 years, delivery at an earlier gestational age, and delivery by emergency CS was closely associated with neonatal respiratory morbidity. Emergency cesarean section was also associated with an increased length of hospitalization (p=0.045) and an increased need for postoperative antibiotics (p=0.0065) compared with an elective cesarean birth.

In conclusion, they found that the risk of NRM in twins born beyond 37 weeks of gestation was rather low. Including all forms of delivery, they found a negligible rate of 0.27% of RDS and 1.61% of TTN, Figure 33. Based on this, they suggested considering elective cesarean delivery at completion of 37 weeks in twins.

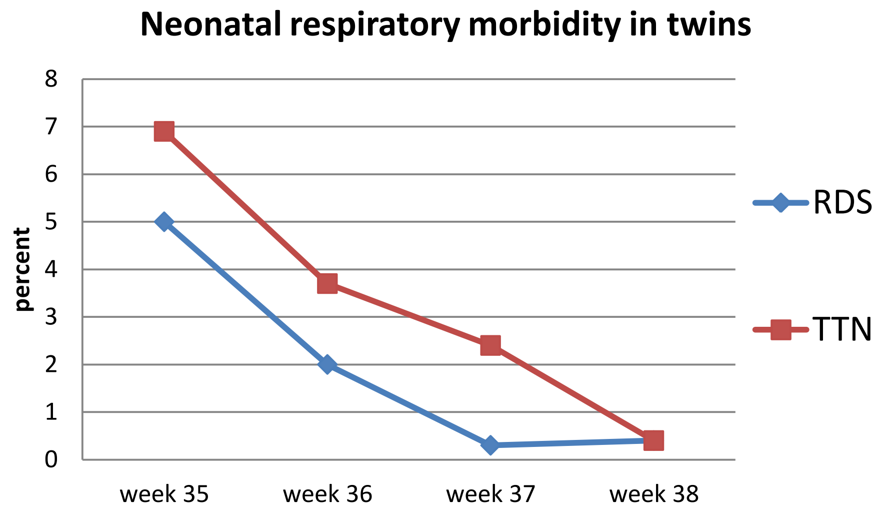


Figure 33 - Risk of neonatal respiratory morbidity (RDS and TTN) in twins born beyond 35 wks expressed as % of twin neonates, respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN).

Adapted from Zipori et al. [133]. *Optimizing outcome of twins by routine cesarean section beyond 37 weeks.* Am J Perinatol. 2011;1:51–56.

According to the Bulletin of the Practice Committee by the American Society for Reproductive Medicine published in 2012 [7], 50% of the twin pregnancies delivered with less than 37 weeks, such that the remaining 50% were undelivered at this gestational age, Table 11.

Table 11 - Maternal complications comparing twins and singletons.

Adapted from Practice Committee of the American Society for Reproductive Medicin [7]. *Multiple gestation associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion.* Fertil Steril 2012; 97:825-834

Maternal complications	**Singletons**	**Twins**
Preeclampsia	6%	10-12%
Gestational diabetes	3%	5-8%
Preterm labor	15%	40%
Delivery at <37 wks	10%	50%

There is no consensus regarding the optimum **mode of delivery** twins. When the presenting twin is not in vertex presentation or the mother had a previous uterine scar, cesarean section is usually the preferred mode of delivery. For the remaining twins who reach 37-38 weeks, there are three options:

- Perform an elective cesarean section
- Await spontaneous labor with the risks of IUFD
- Induce labor as in singletons [123]

RCOG reported one Randomized Control Trial [124] that examined the role of induction of labor with oral prostaglandins in comparison with expectant management with continued surveillance (consisting of daily non-stress testing, twice weekly ultrasound evaluation, and cervical assessment). The study was unable to detect any difference in perinatal mortality rates, a fact most likely caused by the small number of cases (17 inductions vs. 19 expectant managements). However, there was an increase in meconium-stained liquor in the expectant-management group (13% vs. 0%) which could be related to the higher gestational age at delivery for this group.

Even spontaneous labor in twin gestations may be associated with dysfunctional labor or rupture of membranes without contractions, so both augmentation and induction of labor has received renewed interest owing to the rate of cesarean deliveries and the problems with the rising costs of labor management [125].

Several methods of labor inductions in twins have been used over time, including: diluted intravenous oxytocin as in singletons, the use of a catheter balloon [126], prostaglandin preparations [124] and misoprostol [129,130].

Taylor et al. [127], in a paper published in 2012, compared induction of labor in twins with induction of labor in singletons and found that the likelihood of cesarean delivery did not differ between the groups (19% in twins compared with 21% in singletons, p=0.724) nor did the time from induction to vaginal delivery (median interquartile time 9.7(5.5–12.5) hours in twins compared with 10.4 (6.6-14.1) hours in singletons, p=0.255). Results were not different when they looked at nulliparous patients only or multiparous patients only. For an adjusted analysis of risk factors for cesarean delivery in patients undergoing induction, twin pregnancy was not independently associated with cesarean delivery, so they concluded that patients with twin pregnancies undergoing induction of labor have a similar risk of cesarean delivery and a similar length of labor as patients with singleton pregnancies undergoing induction of labor.

Hoffmann et al. [131] analyzed a Danish Population-based retrospective cohort of 1,175 twin pregnancies delivered with 36 weeks or more weeks of gestation. From these, 1,060 (90%) were DC twins and 115 (10%) were MC twins. They defined four groups:

- DC with planned caesarean delivery;
- DC with planned vaginal delivery;
- MC with planned caesarean delivery;
- MC with planned vaginal delivery.

After this, they analyzed the cohort according to chorionicity and mode of delivery, defining a poor outcome as: five minute Apgar score ≤7, umbilical artery pH < 7.10, admission to neonatal unit for more than three days or death.

Hoffmann et al. [131] noticed that DC twins with intended vaginal delivery (*n* = 689), compared with DC twins with planned CS (n = 371), had an increased risk of poor outcome (OR 1.47, p=0.037) after adjustment for body mass index, parity and weight discordance, Table 12. There was no increased risk for poor outcome in MC twins with intended vaginal delivery (n = 63) compared with planned CS (n=52) OR 0.87 95%CI (0.26–2.96). Nulliparity also increased the risk of poor outcome in DC (OR 1.5, p = 0.03) and in MC twins (OR 4.01, p = 0.02), as well as birthweight discordance >300 g (DC, OR 1.50, p = 0.02; and MC, OR 6.02, p=0.002).

For DC twins, there was a significantly higher risk of a poor outcome for the second-born twin compared with the first one (OR 1.64, p = 0.001), Table 13. However, induction of labor did not seem to worsen the outcome for vaginally delivered newborns, either for DC or for MC twins.

Table 12 - Perinatal outcome measured as umbilical pH, Apgar score, admission to NICU ≥3days, neonatal death and all outcome pooled to poor outcome: vaginally delivered DC twins versus DC twins with planned CS and vaginally delivered MC twins versus MC twins with planned CS

Adapted from :Hoffmann et al. [131]. *Twin births: cesarean section or vaginal delivery*? Acta Obstet Gynecol Scand 2012; 91:463–469

	MC intended vaginal delivery (n=63)N(%)	**MC intended CS delivery (n=52) N(%)**	**DC intended vaginal delivery (n=689)N(%)**	**DC intended CS delivery (n=371) N(%)**	**CS vs. Vaginal delivery for DC OR(95%CI)**	**CS vs. Vaginal delivery for DC p-value**
Umbilical artery pH<7.1	4(6.3)	0	42(6.1)	3(0.8)	7.16 (2.20-23.36)	0.001
5 min Apgar≤7	5(7.9)	0	25(3.6)	4(1.1)	3.45 (1.19-10)	0.009
Admission to NICU >3days	7(11.1)	8(15.4)	88(12.8)	42(11.3	1.15 (0.78-1.7)	0.489
Neonatal death	0	0	0	2(.5	-	-
Poor outcome*	12(19%)	8(15.4)	129(18.7)	49(13,2)	1.47(1.02-2.13)	0.037

*Cases with pH<7.1,Apgar≤7 or NICU >3 days, or death for at least one of the children.

Table 13 - Risk of pH <7.1, Apgar <7 or admission to NICU for more than 3 days in second-born twins compared with first-born twins.

Adapted from: Hoffmann et al. [131]. *Twin births: cesarean section or vaginal delivery?* Acta Obstet Gynecol Scand 2012; 91:463–469

	Odds ratio (95% CI)	**p-Value**
Dc twins with planned vaginal delivery	1.64(1.19-2.25)	0.001
MC twins with planned vaginal delivery	1.45(0.54-3.90)	0.454
MC elective CS		Not applicable*
DC elective CS	1.30(1.81-2.09)	0.278

*The same number (7) of first and second-born MC twins had poor outcome when delivered by CS

Sau et al. [132] compared the outcomes of 60 sets of MC twins with 218 sets of DC twins and they found a similar rate of CS between both groups (56.6% vs. 53.6% respectively, $p > 0.1$). Although the number of babies with 5-minute Apgar score of less than 7 was significantly higher for vaginally delivered MC twins compared with DC twins (12 versus 3.5%, $p < 0.001$), the umbilical artery pH of <7.2 was similar (20 vs. 13%, $p > 0.05$), as was the admission to the NICU and the neonatal mortality. However, for MC twins, delivery by CS was associated with increased admission to the NICU and neonatal mortality when compared with the vaginal delivery group.

Smith et al. [134], using the Scottish Morbidity Record linked to records from the Scottish Stillbirth and Infant Death Enquiry, studied the association between stillbirth or neonatal death and mode of delivery in 8,073 twin pairs born between 1985 and 2001 at or after 36 weeks of gestation.

They noticed six deaths of first twins and 30 deaths of second twins, OR for second twin 5.00, 95% CI (2.00–14.70). The OR for death of the second twin due to intrapartum anoxia was 21, 95% CI (3.4–868.5).

They found a fourfold increase in the risk of death for the second-born twin delivered vaginally, but induction of labor did not affect this risk. There was a death of either twin in 2 of the 1,472 (0.14%) deliveries by planned caesarean section and 34 of 6,601 (0.52%) deliveries by other means ,$p<0.05$, OR for planned CS 0.26 ,95% CI (0.03–1.03).

In a cohort of 1,475 pregnancies, planned CS was associated with a decreased risk of death for the second born twin, OR 0.26, 95% CI (0.003–1.03) but they estimated that 264 caesarean deliveries, 95% CI: (158–808) would be required to prevent each death.

They concluded that planned CS may reduce the risk of perinatal death of twins at term by approximately 75%, compared with attempting vaginal birth, and that this was principally because it reduced the risk of death of the second twin due to intrapartum anoxia.

Gocke et al. [241] retrospectively evaluated 136 sets of vertex-non vertex twin deliveries. The primary delivery attempt for the second twin was breech extraction, external cephalic version, or CS due to physician preference. When internal podalic version and breech extraction was performed as the first attempt successful vaginal delivery occurred in 96% of patients. Conversely, external cephalic version was successful in only 46% of patients. Combined delivery (vaginal first twin, CS second one) occurred for 39% of the patients who underwent external cephalic version first, in contrast with 4% combined delivery rate for those sets in which breech extraction was the first attempt. Patients with a successful external cephalic version also experienced higher rates of emergent CS due to fetal distress, prolapse of the cord and compound presentation.

Bischop et al. [206], in a systematic review, reported 8 studies [213,214,215,216, 217,218,221,222] which compared vaginal delivery with CS for non-cephalic presenting twins and concluded that their results do not suggested benefit of CS over vaginal delivery for selected twin pregnancies with the first twin and or the second twin in non-vertex presentation [219,220]. However, it is important to note that some of the studies included in the review were performed many years ago and in countries with little medical litigation.

Conversely, in Paris in 2006, Bats et al. [223] analyzed 166 twin pairs with a non-vertex first twin. Among these, 105 cases (63.3%) had an attempted vaginal delivery, which was successful in 46 cases (43.8%). They did not find a significantly different low neonatal outcome and maternal morbidity for the attempted vaginal group, compared with the planned CS group (n=61 cases). They concluded that their results could be extrapolated to other centers, but that it was important to apply a careful protocol to decide the mode of delivery and the labor practices.

In 2013, Barret et al [240] randomly assigned women between 32 weeks 0 days and 38 weeks 6 days of gestation with twin pregnancy and with the first twin in the cephalic presentation to two groups: planned CS or planned vaginal delivery with CS only if indicated. A total of 1,398 women were randomly assigned to planned CS delivery and 1,406 to planned vaginal delivery. Elective delivery was planned between 37 weeks 5 days and 38 weeks 6 days of gestation. The primary outcome featured as a unit of analysis a composite of fetal or neonatal death or serious neonatal morbidity in the fetus or infant.

The rate of CS delivery was 90.7% in the planned CS delivery group and 43.8% in the planned vaginal delivery group. There was no significant difference in the composite primary outcome between both groups (2.2% versus 1.9%), OR1.16, 95% CI (0.77-1.74) p=0.49. They concluded that, in twin pregnancy, between 32-38 weeks 6 days of gestation, with the first twin in a vertex presentation, planned CS delivery did not significantly decrease or increase the risk of fetal or neonatal death or serious neonatal morbidity, when compared with planned vaginal delivery.

It is evident that not all twin pregnancies are candidates for vaginal delivery or labor induction, and the obstetrical decision for an elective cesarean section is usually primarily related to fetal malpresentation, with a combination other than vertex-vertex twins. However, it is important to note that the presentation of the second twin changes in up to 20% of the cases following the delivery of the first twin [138]. It also seems that both patients and their caregivers are more reluctant to choose labor induction and a vaginal delivery in non-spontaneous twin gestations. This trend, namely cesarean section for 'premium' twin pregnancies, is quite reasonable given the impact of the history of sub-fertility on decision making during labor and delivery [128]. It is important to point out that no solid data exist to show a disadvantage of a planned cesarean birth for twins [128]. However, from a maternal viewpoint, CS has a higher morbidity, mortality [136] and may condition the reproductive future of the women, when compared with vaginal delivery.

O'Neill et al.[233] analyzing the risk of stillbirth in a subsequent pregnancy in women with a previous CS estimated that CS delivery compared to vaginal delivery may increase the risk of stillbirth by 23%.

Leth et al. [139] compared the risk of postpartum infections within 30 days after vaginal birth, emergency, or elective CS in a cohort study in Denmark, considering a total of 32,468 women who gave birth during the period 2001-2005. They found that the risk of postpartum infection seems to be nearly five-fold increased after CS compared with vaginal birth and concluded that this may be of concern since the prevalence of CS is increasing.

Assessment of short term complications of CS may not demonstrate the actual risk. A cesarean scar is known to be associated with higher incidence of placenta previa and morbid placental adherence. A retrospective cohort study of 399,674 women [140] analyzed the rate of placenta previa at second birth for women with vaginal first births and found a rate of 4.4 per 1000 births, compared to 8.7 per 1000 births for women with CS at first birth. After adjustment, CS at first birth remained associated with an increased risk of placenta previa, OR 1.60; 95% CI (1.44- 1.76). In the meta-analysis of 37 previously published studies from 21 countries (140), the overall pooled random effects OR was 2.20, 95% CI (1.96-2.46).

There is also an increased risk of bladder and bowel injury in the event of the women requiring further abdominal or vaginal surgery. Furthermore, a policy of planned cesarean section for twins might increase the risk of neonatal respiratory distress syndrome even if the pregnancy is at or near term. Chasen et al. [137] found that neonatal respiratory disorders were more common in twin pregnancies with caesarean delivery performed before labor and before 38 weeks.

Mauldin et al. [209] compared the route of delivery for twin gestations longer than 35 weeks including cost in the outcomes. From a cohort of 84 vertex- non vertex twin pregnancies, three groups were evaluated: Group A consisting of spontaneous vaginal delivery of the first twin and breech extraction of the second one; Group B, consisting of spontaneous delivery of the first twin and external cephalic version of the second one; Group C, in which both twins underwent a CS. Maternal hospital charges were $5890, $8638 and $7814 for each group, respectively. They noted that all patients in Group A delivered vaginally; conversely, 11 of 19 patients in Group B were delivered by combined delivery. Regarding neonatal outcomes, neonates from Group A had significantly fewer pulmonary complications.

It is important to notice that the delivery of twins is a high risk event and if we choose to deliver twins vaginally we need acknowledge the fact that such a procedure needs a dedicated obstetrical team and close observation throughout the entire process, as well as during labor and delivery. We need physicians skilled in obstetric maneuvers such as breech delivery or breech extraction, a dedicated nursing staff, the availability of pediatric and anesthesia support and continuous fetal monitoring.

Chapter III. Aims

III. <u>Aims</u>

The literature features plenty of studies on the subject of multiple gestations, some of them with conflicting results and conclusions. The evaluation of the results of the Twin Outpatient Consultation at Maternidade Dr. Alfredo da Costa was always a self-imposed duty. From the beginning, all cases of multiple pregnancies were numbered and carefully registered, first on paper, and later on a digital database. As our experience progressed, and our database expanded, we began publishing our results.

1. The presence of an inter-twin discrepancy in an ultrasound report frequently leads to changes in the follow-up schemes and in the time and mode of delivery. However, after elective delivery justified by this pathology, newborns sometimes do not present any inter-twin discrepancy in birth weight. Even worse, large birth weight discordance is sometimes found at birth without previous suspicion. Unlike in singletons, symphysis-fundal height measurements are not effective in identifying growth problems in twins [251], and serial ultrasound scans are required instead [252].

   At the time of the study, several sonographic measurements had been used since the clinical implications of this obstetrical problem first became obvious. Estimated fetal weight (EFW) was the preferred measurement for comparing twins' growth and to predict inter-fetal discrepancy. Several twin pairs were delivered preterm because EFW suggested the presence of a severe inter-twin discordance (>25%).

   The aims of our first paper, **"Abdominal circumference ratio for the diagnosis of inter-twin birth weight discordance",** were:

   a. To determine the accuracy of global sonographic measurements on the diagnosis of discrepant growth in twins
   b. To find the most reliable measurement to predict severe inter-fetal discrepancy (>25%).

c. To establish whether EFW and abdominal circumference (AC) are able to diagnose twin pairs in which the smaller one is small for gestational age (SGA)?

Presently, monitoring the fetal growth in twins is still essential in their surveillance, as it is clear that inter-twin discordance is a sign of fetal distress and could have dire consequences for both twins, especially in monochorionic pregnancies. Further, about 16% of twin gestations are complicated by an inter-twin discordance of at least 20% [28].

2. "What is the normal weight gain during a twin pregnancy" is a staple question posed by patients at the beginning of the follow up. The answer typically given was often the same for obese and underweight women. It is a popular belief in Portugal that pregnant women should eat for two, implying women with twins should eat for three! Fortunately, in our days, women care about their image and they do not accept a hipercaloric diet if they do not need it. At MAC we usually only prescribe a dietary intervention in underweight or obese women.

   The aims of the second paper, **"Perinatal Outcome and Change in Body Mass Index in Mothers of Dichorionic Twins: A Longitudinal Cohort Study"** were:

   a. To analyze the effect of different weight gains in mothers carrying DC twins who did not receive any dietary intervention
   b. To evaluate the average change in weight (%) from the pre-gravid value by trimester using the body mass index (BMI)
   c. To determine whether mothers with an above average change in pre-gravid BMI showed improvements in total twin birth weight or in gestational age at delivery.

Determining the appropriate weight gain in singleton and twin pregnancies remains a very important issue, given that a suitable weight gain reduces: the risk of labor before 36 weeks, the risk of low birth weight, neonatal morbidity and the costs associated with twin gestations [158].

3. Gestational diabetes mellitus (GDM) occurs in multiple pregnancies more often than it does with singletons. Older, pregravid obesity and increased weight gain during pregnancy are known risk factors. However, little information exists about the influence of the presence of GDM in twin pregnancy outcomes.

   The aims of the third paper, **"Gestational diabetes mellitus complicating twin pregnancies"** were:

   a. To identify the risk factors associated with GDM in twin pregnancies
   b. To determine if the outcomes of twin pregnancies with GDM were worse than the ones with no GDM

   Gestational diabetes is still an area in need of further research, as there is conflicting evidence about the occurrence of GDM in multiple gestation, as well as uncertainty as to when during pregnancy we should screen.

4. MC pregnancies account for a significant proportion of perinatal morbidity and mortality in twins, with intrauterine fetal death constituting a major problem. MAC, as a referral Center, has a large database on this kind of multiples. As such, when the controversy on the optimal time of delivery for MC twins appeared we contributed with our own experience.

   The aims of the fourth paper, **"Prospective Risk of Intrauterine Death of Monochorionic Diamniotic Twins"** were:

a. To calculate the prospective risk of fetal death in MC twins
b. To establish the optimal timing of delivery for this kind of twin pregnancies.

The question of when to deliver MC-DA twins is, to this day, a source of controversy. This paper was cited by at least 51 publications since it was published, 19 since 2012. It was the first paper to suggest that MC-DA did not necessarily require delivery at 32 wks by cesarean section, and it remains relevant to today's policies.

5. A proper surveillance of multiples pregnancies decreases premature delivery and ensures that more twin gestations reach 37 weeks without delivery. Labor induction with the use of misoprostol is usually performed in singletons, but few reports about its use in twins existed. The aims of the fifth paper, **"Induction of Labor with Misoprostol in Nulliparous Mothers of Twins"** were:

    a. To evaluate the efficacy of labor induction in twin pregnancies
    b. To evaluate the safety of this pressure using misoprostol

    Determining the situations in which twins should be induced remains an important question today. About 50% of twin gestations reach the 37 week mark, thus incurring the associated risks. In these situations, labor induction offers reduced risks for the twins without an associated increase in maternal risks when compared to waiting for spontaneous labor.

6. Elective CS is the most frequent mode of delivery in twins, usually because of fetal malpresentation or the existence of a previous uterine scar. However, elective CS in twin pregnancies is now often the patient's choice, a result of complacency on the part of the medical teams. One

of the arguments for the choice of elective CS is that CS in labor is recognized to have more morbidity to the women.

The aims of the sixth paper, **"Puerperal complications following elective caesarean sections for twin pregnancies"** were:

a. To estimate the maternal puerperal morbidity in elective CS in twins
b. To estimate the maternal puerperal morbidity in emergency CS in twins.
c. To evaluate if there are disadvantages associated with planned CS in twins

Twin pregnancies are often a result of several infertility treatments. An increasing number of couples wants fewer children and, in the presence of a multiple pregnancy, want to deliver in the safest way. Therefore, knowing how to deliver twins remains a crucial subject in the profession.

Chapter IV. Published Studies

IV. Published Studies

In agreement with the *Decreto-Lei 388/70, artigo 8º, paragraph 2*, the results presented and discussed in this thesis were published in the following scientific peer-reviewed journals:

1. Simões T, Julio C, Cordeiro A, Cohen A, Silva A, Blickstein I, ***Abdominal circumference ratio for the diagnosis of intertwin birth weight discordance***. J.Perinat Med 2011;39: 43–46

2. Simões T, Cordeiro A, Júlio C, Reis J, Dias E, Blickstein I. ***Perinatal Outcome and Change in Body Mass Index in Mothers of Dichorionic Twins: A Longitudinal Cohort Study.*** Twin Res Hum Genet. 2007;11:219-223

3. Simões T, Queirós A, Correia L, Rocha T, Dias E, Blickstein I. ***Gestational diabetes mellitus complicating twin pregnancies.*** J. Perinat Med. 2011; 39:437–440.

4. Simões T, Amaral N, Lerman R, Ribeiro F, Dias E, Blickstein I***. Prospective Risk of Intrauterine Death of Monochorionic Diamniotic Twins.*** Am J Obstet Gynecol 2006;195:134-139

5. Simões T, Condeço P, Dias E, Ventura P, Matos C, Blickstein I. ***Induction of Labor with Misoprostol in Nulliparous Mothers of Twins.*** J.Perinat Med. 2006;34:111-114

6. Simões T, Aboim L, Costa A, Ambrosio A, Alves S, Blickstein I**. *Puerperal complications following elective caesarean sections for twin pregnancies*.** J. Perinat Med. 2007; 35:104-107.

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Original article – Fetus

Abdominal circumference ratio for the diagnosis of intertwin birth weight discordance

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Abstract

Objectives: We assessed the accuracy of predicting severe twin birth weight discordance (>25%) using the estimated fetal weights (EFW) and abdominal circumference (AC) ratio.

Method: A cohort of twin gestations underwent ultrasound examinations within two weeks from birth. We focused on the accuracy of EFW and on the diagnosis of severe birth weight discordance by the difference in EFWs and the AC ratio.

Results: The 661 eligible twin pairs included 51 (7.7%) severely discordant pairs. The accuracy of an EFW to predict the actual birth weight was quite poor, with an acceptable specificity (96.4%), but low sensitivity (28.6–40.5%), to detect severely discordant pairs, whereas an AC ratio of 1.3 detected these discordant pairs with sensitivity and specificity of 97.3–100% and 99.6–99.7%, respectively.

Conclusion: By comparing EFWs, 59.5–71.4% of discordant pairs >25% are missed, whereas an AC ratio >1.3 would identify almost all cases.

Keywords: Abdominal circumference ratio; birth weight discordance; estimated fetal weight; twins; ultrasound.

Introduction

The prenatal diagnosis of growth discordant twins was attempted since the early days of ultrasonography. For example, in 1977 Houlton compared the biparietal diameters (BPD) in 28 pairs and was able to detect divergent growth in 61% of the pairs [13]. In the following three decades, during which the clinical implications of discordant growth of twins has been clarified [3], fetal weight discordance became an integral part of the prenatal assessment of twins. These attempts are apparent from hundreds of studies trying to establish the accuracy of sonographic prediction of birth weight discordance. At present, the best estimate of discordant growth comes from calculating paired estimated fetal weights (EFWs) and deriving the discordance level by the same way it is derived from actual birth weights [5]. At the same time, however, it became clear that even with a relatively accurate EFW (within ±10% of the actual birth weight) calculated for each fetus, the ''±'' situation may involve significant error in estimating birth weight discordance with both ''diverging'' and ''converging'' estimations.

Over the years, two more related issues became apparent [4]. First, that lower levels of birth weight discordance probably represent an intertwin natural variation and that the level likely to represent aberrant growth is at least 25% [8]. Second, that as many as 40% of severely discordant twins (i.e., birth weight discordance >25%) do not represent significant growth restriction because the smaller twin is not small-for-gestational age (SGA, birth weight $<10^{th}$ percentile for gestational age) [1, 6]. It follows that once discordant growth is suspected, one should differentiate between the ''normal'' and the ''abnormal'' (i.e., with and without the smaller twin being SGA) severely discordant pairs. Currently, there are no data to show how accurate are sonographic measurements in identifying these abnormally discordant pairs.

One way to reduce the inherent method error of estimating intertwin discordance was to compare the abdominal circumference (AC). In the mid-80s several AC differences were suggested as adjuncts to the EFW difference to detect discordant twin growth [7, 15]. However, the absolute AC difference seems to be gestational age dependant and, therefore, could not significantly improve the accuracy of estimating birth weight discordance [9]. More recently, a Canadian study [14] calculated the AC ratio in a cohort of diamniotic twin gestations. A total of 64 pregnancies (12.7%) had discordant birth weights >25% and an AC ratio cut-off of 0.93 yielded a sensitivity and specificity of 61% and 84%, respectively.

In the present study, we assessed the accuracy of the AC ratio and the EFW difference in predicting concordant twins, and in differentiating discordant pairs in which the smaller twin was or was not SGA.

Methods

This is a study of sonographic measurements in twins prospectively collected between January 1, 1994 and June 30, 2008 in the tertiary maternity center Alfredo da Costa, Lisbon, Portugal. During this period, information about the pregnancy and delivery was prospectively registered on a preset form and subsequently entered into a computerized system. We included in the present assessment all

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twin gestations irrespective of chorionicity, in which paired sonographic measurements were performed within two weeks before birth and both twins were born alive at our hospital. All other pairs were excluded. During this period, we used several ultrasound machines, but the measurements were performed by the same standardized method and by the same operators (Portuguese authors). EFW was calculated automatically by the sonographic machine using the ASTRAIA software (Astraia software GmbH, Munich, Germany) and the inbuilt formula of Hadlock (based on AC and femur length). The AC was measured at the level of the bifurcation of the main portal vein, taking care of depicting as round a section as possible. Measurements of each parameter were done three times and the average was used for calculations. In this study, twin A was the presenting twin.

This study focused on three questions. (1) The accuracy of EFW as compared to the actual birth weight for each of the twins. We defined an accurate EFW as one within ±10% from the actual birth weight, and calculated the frequency of an EFW exceeding this value. (2) The predictive values of the difference in EFWs to establish an accurate diagnosis of severe (>25%) birth weight discordance. (3) The accuracy of the AC ratio (AC of larger twin/AC of smaller twin) in predicting birth weight discordance. We evaluated three ratios: >10% difference (ratio >1.1), >20% difference (ratio of >1.2), >30% difference (ratio of >1.3). The primary hypothesis was that the AC ratio might be a better predictor of severe discordance.

Discordance level was calculated from the difference between EFWs or birth weights divided by the EFW or birth weight of the larger twin and expressed as a percentage. The severely discordant pairs were further subdivided into pairs in which the smaller twin was either SGA (SGA discordant) or not SGA [appropriate-for-gestational age (AGA) discordant]. SGA status was calculated from Portuguese twin birth weight by gestational age charts (unpublished). The study was approved by the local Institutional Review Board.

We used the True EPISTAT Software (Math Archives, Round Rock, TX, USA) to compare frequencies by the Fisher's exact. We derived odds ratio (OR) and Corenfield's 95% confidence intervals (CI). Continuous variables were compared by Student's *t*-test, with P-value <0.05 considered significant. Sensitivity was calculated from the number of true positive values divided by the sum of true positive plus and false negative values, whereas specificity was calculated from the number of true negatives divided by the sum of true negative and false positive values.

Results

The results from 661 twin pairs were eligible for the study, comprising 610 concordant (<25%) and 51 (7.7%) severely discordant pairs. Table 1 shows that pregnancies with concordant pairs had similar characteristics compared to pregnancies with AGA discordant twins. In contrast, SGA discordant pairs had a significantly lower (P<0.05) mean maternal age, mean gestational age of last sonography, and mean gestational age at birth compared to both concordant and AGA discordant pairs.

Table 2 shows that the accuracy of an EFW to predict the actual birth weight was poor for twin A with significantly more AGA discordant twins being wrongly estimated (>10% of actual birth weight) compared to the other two groups. These values were somewhat better for twin B with about 50% accurate EFWs in all three groups. Whereas the specificity was quite good to detect both groups of discordant pairs, the sensitivity was quite low.

Table 3 shows the accuracy of the three AC ratios in predicting discordance. It appears that almost half of the concordant twins have at least a 10% difference (AC ratio of 1.1). When a higher cut-off value was chosen (i.e., ratio of 1.2 and 1.3), both sensitivity and specificity reached nearly 100%.

Discussion

The prediction of intertwin birth weight discordance by sonography has been extensively studied [5]. Discordance, especially if severe, seems to be a trigger for looking at growth aberration of the twins, and in particular, growth restriction of the smaller twin. Very different predictive results can be found among the numerous papers, but the overall impression is that prediction of discordant growth by comparing EFWs is not accurate for clinical use [4, 5]. This statement is based on two observations. First, probably because of fetal crowding in twin gestations, it seems more difficult to obtain an accurate EFW for an individual twin compared with singletons [12]. This observation was supported by our study (Table 2). Second, even with accurate EFWs (i.e., within ±10% from the actual birth weight) it is inherently difficult to obtain an accurate discordance level. The decade-old conclusion reached in the review of Caravello and co-workers, is still relevant today: most popular methods (difference in AC or EFW) for predicting discordant growth in twin gestations have limited accuracy for discor-

Table 1 Maternal age and gestational age at last sonography and at birth.

	Concordant	Discordant (>25%)	
		AGA	SGA
n (%)	610 (92.4)	14 (2.1)	37 (5.6)
Mean maternal age (years)	30.4±5.2	30.5±4.7	27.8±4.6[a]
Gestational age at last sonography (weeks)	34.0±2.4	34.0±1.3	32.6±2.6[a]
Gestational age at birth (weeks)	35.6±2.2	35.7±1.0	33.5±2.7[a]

Data presented as mean±standard deviation.
[a]SGA discordant twins vs. concordant and AGA discordant twins, P<0.05.
AGA=appropriate-for-gestational age, SGA=small-for-gestational age.

Table 2 Estimated fetal weight (EFW) difference in predicting birth weight discordance.

	Concordant (n=610)	Discordant (>25%)	
		AGA (n=14)	SGA (n=37)
EFW, twin A (g)	2104±486	2168±314	1739±520
Birth weight, twin A (g)	2316±466	2824±545	1907±513
Accurate EFW (<10% error)	310/610 (50.8)[a]	2/14 (14.3)[a,b]	15/37 (40.5)[b]
EFW, twin B (g)	2145±483	2175±462	1529±484
Birth weight, twin B (g)	2274±470	2328±401	1565±537
Accurate EFW (<10% error)	330/610 (54.1)	6/14 (42.8)	18/37 (48.6)
Estimated discordance <25%	588 (96.4)	10 (71.4)	22 (59.4)
Estimated discordance >25%	True negative, 22	True positive, 4	True positive, 15
Sensitivity (%)		28.6	40.5
Specificity (%)		96.4	96.4

Data presented as n (%) and as mean±standard deviation. Predictive values were calculated by separate comparisons of AGA and SGA discordant to concordant twins.
[a]OR 0.2, 95% CI 0.04, 0.8.
[b]OR 0.1, 95% CI 0.01, 0.8.
AGA=appropriate-for-gestational age, SGA=small-for-gestational age, OR=odds ratio, CI=confidence interval.

dance level of at least 25% [10]. It is, therefore, necessary to find ancillary means to improve the prediction of discordance.

In our sample of twins a ratio of 1.3 between paired ACs predicts severe birth weight discordance with very high sensitivity and specificity values. Our cut-off AC ratio is different than that proposed by Klam et al. [14], but we obtained much higher sensitivity and specificity values compared to those found by these authors. Moreover, this ratio was as good in predicting severely discordant pairs with and without an SGA smaller twin. Thus, although this ratio is an excellent predictor of severe discordance, it cannot differentiate between the two entities.

One limitation of our study is the low frequency of severe discordance (7.7%). This value, however, is in accord with the frequencies found in nearly 125,000 American twin pairs [5] but reduces the power of the analysis. On the other hand, our study is among the largest of its kind, and comes from a single center, with a protocol of ultrasound assessment that did not change over time.

Table 3 Abdominal circumference (AC) ratio predicting birth weight discordance.

	Concordant (n=610)	Discordant (>25%)	
		AGA (n=14)	SGA (n=37)
Ratio >1.1	253	9	23
Sensitivity (%)		58.5	31.8
Specificity (%)		35.7	37.8
Ratio >1.2	4	14	32
Sensitivity (%)		100	86.5
Specificity (%)		99.3	99.3
Ratio >1.3	2	14	36
Sensitivity (%)		100	97.3
Specificity (%)		99.6	99.7

Data presented as n (%). Predictive values were calculated by separate comparisons of AGA and SGA discordant to concordant twins. AGA=appropriate-for-gestational age, SGA=small-for-gestational age.

Another limitation of our study, as in most other studies, is that all methods for estimating discordance are in fact capturing the situation at a stage within one to two weeks from birth. Such methods, in fact, do not predict severe discordance but rather diagnose it before birth. Attempts to predict discordance by ultrasound measurements of fetal growth velocity and size during the early weeks of the third trimester were poor predictors of birth weight discordance [2, 11]. Although Hadlock's formula using the femur length and AC might underestimate the true birth weight, it is expected to do so for both twins and thus unlikely to reduce the accuracy of estimated discordance.

The question may arise if such a diagnosis is not reached too late, and hence there is need to assess the ability of the AC ratio obtained in the early third trimester to predict the subsequent development of severe discordance. It is also possible that fetuses may continue to grow in the last two weeks before birth and therefore reduce the accuracy of predicting discordance. However, we feel it is unlikely that a difference generated within the last two weeks will cause severe discordance in mildly discordant twins or would mistakenly consider one twin as SGA. Using the extremes (severe discordance and being SGA) may decrease the potential methodological inaccuracy. Because we used the last sonographic measurement, we were unable to count how many pairs were close to but less then 25% discordance at two weeks before birth but were discordant at birth. Thus, counting them as false negative cases might be incorrect given the potential for a true diagnosis had another measurement been done.

Regardless of these reservations, our data suggest that with the current method of comparing EFWs, 60–70% of severely discordant pairs are missed, whereas the finding of an AC ratio >1.3 would identify almost all cases.

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Perinatal Outcome and Change in Body Mass Index in Mothers of Dichorionic twins: A Longitudinal Cohort Study

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We used a prospective cohort to analyze the effect of change in BMI rather than change in weight, in mothers carrying dichorionic twins from a population that did not receive any dietary intervention. A total of 269 mothers (150 nulliparas and 119 multiparas) were evaluated. The average change (%) from the pre-gravid BMI was 7.2 ± 6.1, 17.4 ± 8.2, and 28.7 ± 10.8, at 12–14, 22–25, and 30–34 weeks, respectively, without difference between nulliparas and multiparas. The comparison between maternities below or above the average change from the pregravid BMI failed to demonstrate an advantage (in terms of total twin birthweight and gestational age) of an above average change from the pregravid BMI, even when the lower versus upper quartiles were compared. Our observations reached different conclusions regarding the recommended universal dietary intervention in twin gestations. A cautious approach is advocated towards seemingly harmless excess weight gain, as normal weight women may turn overweight, or even obese, by the end of pregnancy, and be exposed to the untoward effects of obesity on future health and body image.

Preterm birth and low birthweight are the most significant complications of twin gestations. In the United States, more than one of every four very low birthweight (VLBW) infants (< 1500 g) comes from a multiple birth (Martin et al., 2005), and nearly one of every five deaths within the first month of birth were born in a multiple delivery (MacDorman et al., 2005). Specifically, the 2002 clinical statistics from the United States suggest that as many as 58.2% and 11.9% of twins are born preterm (< 37 weeks) and very preterm (< 32 weeks), respectively, and as many as 55.4 % and 10.2%, respectively, are low (< 2500g) or very low (< 1500g) birthweight infants. (Martin et al., 2003) These figures suggest that more risky groups of infants — those delivered very preterm and/or with a VLBW — are roughly 7 to 9 times more prevalent among twin than among singleton gestations (Martin et al., 2003). The significant contribution of twins to overall preterm and low birthweight rates is further emphasized by the fact that birth rates of twins are still increasing, as opposed to the stabilized or even decreasing birth rates of higher-order multiples (Blickstein & Keith, 2005).

Regrettably, there are no practical means to reduce these adverse outcomes of twin pregnancies to the comparable singleton levels. Indeed, it seems unrealistic to expect that twin births would have similar outcomes to singleton births. A more realistic approach would be to focus on methods that may reduce the more risky subgroup of twins, namely to reduce the rates of very preterm and VLBW infants. In this respect, the seminal work of Luke and her coworkers seems to be of utmost importance. In both retrospective and prospective cohorts, Luke and her colleagues observed a significant increase in birthweight and gestational age in twins whose mother gained enough weight during early (up to 24 weeks) pregnancy. (Luke et al., 1991; Luke et al., 1993; Luke & Leurgans, 1996; Luke et al., 1997; Luke, 1998; Luke et al., 1998; Luke, Hediger et al., 2003). The general consensus among researchers who have evaluated these twin guidelines is that to qualify as ‘enough’, total weight gain should be at least 40–45 pounds (18–20 kg), with an emphasis on adequate weight gain before 24 weeks’ gestation (Luke, Brown et al., 1998)

In a recent prospective intervention study, Luke, Brown et al. (2003) observed that pregnancies in women who participated in a specialized program, which included twice-monthly visits, dietary prescription of 3000 to 4000 kcal per day, multimineral supplementation, and patient education, were associated with improved pregnancy outcomes, and lower neonatal morbidity, and consequently reduced cost per twin compared to nonparticipants.

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Despite the potential benefit attributed to dietary intervention as an important method of improving the outcome of multiple births, care should be taken in interpretation of the data that led to the recommended weight gains. In particular, it should be noted that in many instances, extrapolations of weight gain, rather than actual weight gain measurements in each period of gestation, were used (Luke et al., 1991; Luke et al., 1993; Luke & Leurgans, 1996; Luke et al., 1997; Luke, 1998; Luke et al., 1998; Luke, Hediger et al., 2003; Luke, Brown et al., 2003; Flidel-Rimon et al., 2005). It should also be noted that outcomes may differ according to the method used to estimate weight gain, by the potential confounding effect of prepregnancy maternal weight and body mass index (BMI; Luke, Hediger et al., 2003; Luke, Brown et al., 2003; Flidel-Rimon et al., 2005; Flidel-Rimon et al., 2006), as well as by the confounding effect of unrecognized dietary intervention (Luke, Brown et al., 2003), and chorionicity.

In order to circumvent these potential confounders, we used a prospective cohort to analyze the effect of the change in BMI in mothers carrying dichorionic twin gestations in a population that did not receive any dietary intervention. This approach, namely, the change in BMI rather than the change in weight, has not been previously assessed in a prospective cohort.

Material and Methods

During the period September 1994-March 2006, we followed and delivered 946 twin pregnancies at the Maternidade Dr. Alfredo da Costa, Lisbon, Portugal. This figure represents nearly 1% of all deliveries in this hospital during the study period. During the study, information about the pregnancy and delivery was first registered on a preset form and then entered into a computerized system. Because a significant proportion of pregnancies were referred at an advanced gestational age, complete data relating to maternal height, pregravid weight, and longitudinal weight measurements were available only for 360 mothers who were followed throughout gestation. In order to avoid the confounding effect of chorionicity, which has a significant effect on fetal growth, we excluded monochorionic twins and focused on 281 dichorionic twin gestations.

Pregnancies were grouped by parity (nulliparas and multiparas) and by body mass index (BMI) using the CDC categories of underweight (BMI < 18.5), normal (BMI 18.5–24.9), and overweight/obese (BMI > 25; CDC website). We used the CDC categories because they are the most frequently used values in the literature. BMI was calculated from the formula weight(kg)/(height(m)^2. Following a preliminary assessment of the distribution of BMI, 13 cases of underweight mothers were found and this very small group was also excluded from the analysis.

The following maternal variables were considered in the remaining 268 pregnancies: maternal pregravid weight, maternal height, and maternal weight at each trimester and at birth. Pregravid weight was recorded from referral documentations; maternal height was measured at our service; and finally, maternal weight during each trimester and at birth was recorded from our own measurements (1st trimester 12–14 weeks, 2nd trimester 22–25 weeks, and 3rd trimester 30–34 weeks). When two or more weight measurements were available during a given trimester, an average weight was calculated. All weights were rounded to the first digit.

We derived the BMI-adjusted weight gain, which is defined as the change in BMI between the BMI obtained in a given gestational expressed as a percentage of the pre-gravid BMI (i.e., the larger the percentage the greater the difference in BMI from a given pre-gravid BMI). This method of presentation of weight gains was used because a given weight gain is expected to have a different meaning for different pregravid BMI. The BMI-adjusted weight gain was calculated for each trimester and then correlated with the total twin birthweight (twin A + twin B) and gestational age at birth. These outcome measures were chosen because they are the most likely to be influenced by maternal weight gain. Finally, we derived means and quartiles of the BMI-adjusted weight gain differences to compare the outcome variables between patients above or below the mean, and between patients in the upper and lower quartile. This was done separately for multiparas and nulliparas because parity, per se, is a powerful determinant of birthweight in twins. (Blickstein, 2005).

The data were evaluated using Microsoft Excel and we used True EPISTAT Software (Math Archives, Round Rock, TX) to perform Student's *t* tests for continuous variables. We derived *p* values, and these were considered significant if greater than .05. The study was approved by the local ethics committee.

Results

A total of 269 mothers (150 nulliparas and 119 multiparas) carrying dichorionic twins were evaluated. The mean maternal age was 30.5 ± 5.0 years, the mean height was 162.1 ± 6.7 cm, the mean pregravid weight was 63.8 ± 11.4 kg, and the mean pre-gravid BMI was 24.3 ± 4.3 kg/m^2. By the end of the first trimester, at 12–14 weeks, the average change (%) in pre-gravid BMI was 7.2 ± 6.1, and was similar in nulliparas and multiparas (7.5 ± 6.2 vs. 6.9 ± 5.9, respectively). At around mid-gestation, at 22–25 weeks, the average change (%) in pregravid BMI was 17.4 ± 8.2, and was again similar in nulliparas and multiparas (18.5 ± 7.7 vs. 16.0 ± 8.6, respectively). In the third trimester, at 30–34 weeks, the average change (%) in pregravid BMI was 28.7 ± 10.8, and was once again similar in nulliparas and multiparas (30.2 ± 9.3 vs. 26.7 ± 12.3, respectively). These average changes in BMI increased

Table 1

Comparison Between Below or Above Average Change in BMI on Total Twin Birthweight and Gestational Age, by Gestational Period and Parity

	Nulliparas (*N* = 150)		Multiparas (*N* = 119)	
	Total twin birthweight (g)	Gestational age (weeks)	Total twin birthweight (g)	Gestational age (weeks)
Pregravid BMI				
< average	4742 ± 641	35.8 ± 1.2	4968 ± 595	36.1 ± 1.2
> average	4746 ± 648	35.6 ± 1.5	5129 ± 642	36.4 ± 1.0
Δ BMI at 12–14 weeks				
< average	4807 ± 598	35.8 ± 1.4	5152 ± 568	36.3 ± 1.2
> average	4650 ± 697	35.6 ± 1.4	4861 ± 637	36.1 ± 1.1
Δ BMI at 22–25 weeks				
< average	4792 ± 624	35.8 ± 1.4	5039 ± 590	36.3 ± 1.1
> average	4691 ± 661	35.7 ± 1.4	5007 ± 649	36.1 ± 1.5
Δ BMI at 30–34 weeks				
< average	4707 ± 656	35.5 ± 1.5	5028 ± 571	36.3 ± 1.1
> average	4783 ± 629	35.9 ± 1.3	5021 ± 669	36.1 ± 1.2

Note: Data are shown as mean ± *SD*. No significant differences were found.

Table 2

Comparison Between Lower and Upper Quartiles of the Change in BMI on Total Twin Birthweight and Gestational Age, by Gestational Period and Parity

	Nulliparas (N = 150)		Multiparas (N = 119)	
	Total twin birthweight (g)	Gestational age (weeks)	Total twin birthweight (g)	Gestational age (weeks)
Pregravid BMI				
1st quartile	4813 ± 674	35.9 ± 1.2	4834 ± 612	36.2 ± 1.2
4th quartile	4827 ± 592	35.7 ± 1.4	5049 ± 580	36.3 ± 1.0
Δ BMI at 12–14 weeks				
1st quartile	4772 ± 636	35.5 ± 1.5	5153 ± 440	36.4 ± 0.8
4th quartile	4716 ± 718	35.6 ± 1.4	4908 ± 636	36.2 ± 1.2
Δ BMI at 22–25 weeks				
1st quartile	4813 ± 638	35.9 ± 1.5	5192 ± 485	36.6 ± 0.8
4th quartile	4683 ± 733	35.6 ± 1.5	5030 ± 618	36.1± 1.2
Δ BMI at 30–34 weeks				
1st quartile	4713 ±677	35.6 ± 1.6	5102 ± 558	36.5 ± 0.9
4th quartile	4843 ± 675	36.2 ± 1.3	5051 ± 656	36.2 ± 1.3

Note: Data are shown as mean ± SD. No significant differences were found.

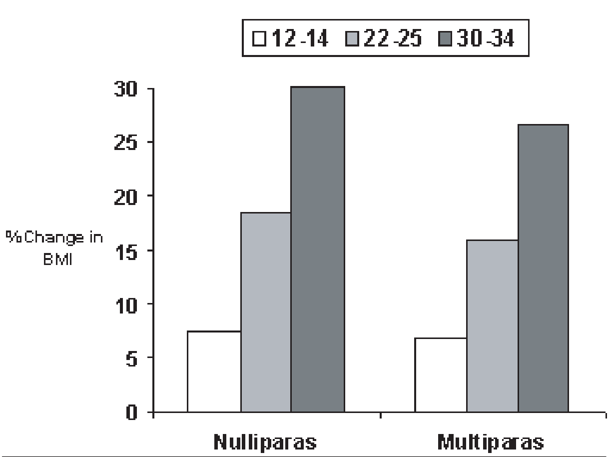

Figure 1

Change in BMI (%) by gestational period (wks) and parity.

in a dose related fashion as pregnancy advanced (Figure 1); in addition, changes in BMI were somewhat higher in nulliparas.

The mean gestational age at birth was 36.0 ± 1.3 weeks, and the total twin birthweight was 4868 ± 644g. Table 1 shows the comparison of these outcome measures between maternities below or above the average change in pregravid BMI. The analysis failed to demonstrate an advantage of an above average change in pregravid BMI. Even when the tails of the distributions (i.e., lower vs. upper quartiles) were compared (Table 2), no significant differences were found.

Discussion

Dietary intervention resulting in maternal weight gain is believed to be the only effective prophylactic treatment which improves outcomes in multiple pregnancies (Luke et al., 1991; Luke et al., 1993; Luke & Leurgans, 1996; Luke et al., 1997; Luke, 1998; Luke et al., 1998; Luke, Hediger et al., 2003; Luke, Brown et al., 2003), although the explanation for this presumable cause-and-effect relationship is still debatable. It seems logical that for adequate growth of more than a single placenta, and for nurture of more than one fetus, additional energy (i.e., caloric) input is required (Blickstein, 2005). However, if this energy is directed to the feto-placental units, maternal weight gain means input of surplus energy. In other words, not only are better outcomes found in cases where food calories are consumed in excess, but also a significant excess of these calories (to produce a significant weight gain) must be present before an effect can be seen. It is therefore plausible in twin pregnancies that maternal weight gain has a significant effect in *a priori* lean mothers compared to mothers who before pregnancy have an appropriate BMI, or are overweight or obese, as has been previously found in triplet gestations. (Flidel-Rimon et al., 2005; Flidel-Rimon et al., 2006).

It is unclear how a net gain in weight is related to outcomes, because energy is simply stored in the body in the form of glycogen and adipose tissue, and is readily transformed back to energy when needed. This accepted mechanism is directly related to probably different biological implications of a given weight gain for different BMIs. Hence, if weight gain were to affect outcomes, it should be tailored to a given pre-gravid BMI.

Explanation of the causal relationship between maternal weight gain and improved outcomes is also somewhat hampered by methodological issues. In almost all the studies in question, weight gain is estimated from an average weekly weight gain, which is calculated from maternal weight at a given gestational age and the pre-gravid weight, followed by extrapolation to 24 weeks' gestation. Such extrapolation is necessary because most large registries do not have longitudinal maternal weight assessments (Flidel-Rimon et al., 2005; Flidel-Rimon et al., 2006), and this method provides the next best estimation. However, the construct of the prospective cohort study conducted by Luke, Brown et al. (2003) could not differentiate between the effects of weight gain per se, and the potentially beneficial effects of close follow up, multimineral supplementation, and patient education (Flidel-Rimon et al., 2006). In addition to these methodological limitations emerging from the need for extrapolation, the unquestionable effects of chorionicity on outcomes are seldom considered in large registries, as chorionicity information is ill-recorded or entirely disregarded. (Flidel-Rimon et al., 2005; Flidel-Rimon et al., 2006). Finally, surprisingly few other studies on the effect of weight gain have been carried out (Rydhstroem & Walles, 1996; Lantz et al., 1996; Yokoyama & Shimizu, 1999; Kanadys & Oleszczuk, 2000).

With these difficulties in mind, we conducted this prospective analysis of the effect of the change in BMI in mothers carrying dichorionic twin gestations in a population that did not receive any dietary intervention. Unlike previous studies, in this cohort we could not find an association between weight gain, in terms of change in BMI, and outcomes, in terms of gestational age at birth and total twin birthweight. Our observations led to different conclusions regarding recommended universal dietary intervention in twin gestations and, therefore, universal recommendations of early weight gain in twins should be confirmed by intention-to-treat, randomized trials.

It should be remembered, however, that we excluded from this study a small number of underweight mothers who might turn out to be the target population for dietary intervention in multiple pregnancies. (Flidel-Rimon et al., 2006). It is thus possible that inclusion of this group of twin mothers would have shown different outcomes (Flidel-Rimon et al., 2005). Additionally, it should be noted that our observations in twins may not apply to triplets, as potential effects of weight gain in higher order multiple pregnancies were not considered in this study.

Finally, the cautious approach that we advocate to the seemingly harmless recommendation of weight gain is best appreciated by the possibility of many normal weight women becoming overweight or even obese by the end of pregnancy, and by the untoward effects of obesity on future health and body image (Flidel-Rimon et al., 2006).

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Gestational diabetes mellitus complicating twin pregnancies

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Abstract

Objective: To compare outcomes of twin pregnancies with and without gestational diabetes mellitus (GDM).

Study design: We compared 105 twin pregnancies with GDM (7.8% of all twin pregnancies) to 315 controls without GDM, matched for gestational age, chorionicity and year of birth.

Results: Pre-gravid obesity appears to predispose women to GDM during twin pregnancy [odds ratio (OR) 3.5; 95% confidence interval (CI) 1.7, 7.0]. Overweight and obese women that subsequently developed GDM during their twin gestation were less likely to conceive spontaneously (OR 0.4; 95% CI 0.3, 0.7). Twins from the GDM group had more respiratory distress syndrome (RDS, OR 2.2; 95% CI 1.3, 3.7) and had a three-fold, but not significantly increased perinatal mortality rate. Birth weight characteristics were similar in both groups.

Conclusion: Twin pregnancies complicated by GDM might be associated with pre-pregnancy maternal obesity and are at increased risk of RDS and non-significant increased risk of perinatal death.

Keywords: Gestational diabetes; obesity; respiratory distress syndrome; twin pregnancy.

Introduction

Gestational diabetes mellitus (GDM) is a relatively common disease. Much information on the clinical significance of GDM in singleton pregnancies but relatively little information exists on the association between gestational diabetes and multiple pregnancy [6]. It has been argued that multiple pregnancies are prone to GDM because of larger placental mass (hyperplacentosis), older age of expecting mothers of multiples, increased weight gain and body mass in twin gestations, and because of exaggerated response to fasting and food [6]. Indeed, Simchen et al. [12] showed that pregnancy in advanced maternal age after ovum donation had, among other complications, 31% of GDM. It also appears that a plurality-dependent frequency of GDM exists whereby GDM was significantly more frequent in triplets compared to (reduced) twins [14]. At the same time, however, conflicting data exist concerning GDM and multiple pregnancies, whereby a similar prevalence of GDM was found in twin and singleton pregnancies, no difference was found in glucose challenge and tolerance tests between twin and singleton pregnancies, and similar insulin requirements were found in twin and singleton pregnancies complicated by GDM [6].

Irrespective of the conflicting views, the increasing numbers of twin pregnancies and births observed in most developed countries increases the number of expecting mothers of twins diagnosed with GDM. Moreover, the few quasi-epidemiological studies describing the prevalence of GDM in twin gestations are quite old and presumably include few multiple pregnancies resulting from iatrogenic conceptions (i.e., after infertility treatment). Also, some bias exists which overlooks changes in management over time. For example, it would be interesting to know how recommendations for excess weight gain during early stages of a multiple pregnancy would influence carbohydrate metabolism [9].

It is also striking that data concerning the effect of GDM on perinatal outcome in multiple pregnancies are very scant. Tchobroutsky et al. [15] reported on a high-frequency of fetal malformations in type I diabetic women with twin pregnancies, however, the small number of cases precluded a final conclusion and are irrelevant for gestational diabetes. Keller et al. [7] compared 13 twin pregnancies complicated with GDM to matched-by-gestational-age twin pregnancies. Within this very small sample size there was a trend of greater likelihoods of respiratory distress syndrome (RDS), hyperbilirubinemia and prolonged neonatal intensive care nursery admission in the diabetic group. More recently, Rauh-Hain et al. [11] compared twin to singleton pregnancies and found that patients with twins had a two-fold increased risk of developing GDM. In terms of neonatal outcome, twins of gestational diabetics had a higher rate of admission to the neonatal intensive care unit, longer hospitalization, and higher risk of RDS.

With these difficulties in mind, we conducted a case-control study to examine the perinatal outcome related to the co-occurrence of GDM and twin gestations.

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Material and methods

During the period January 1, 1999 through September 30, 2010, there were 1346 twin pregnancies followed and delivered after 24 weeks' gestation at the Maternity Dr. Alfredo da Costa, Lisbon, Portugal (a tertiary perinatal center that cares for the Lisbon area, and serves as a referral center for the south of Portugal). This figure represents approximately 2.5% of all deliveries. During this period, information about pregnancy and delivery was registered prospectively on a preset form and subsequently entered into a computerized system. We excluded twin gestations that were delivered only and were not followed at our service.

For this study, we identified twin pregnancies with the diagnosis of GDM, established according to the Carpenter and Coustan criteria [1]. For controls, we matched the remaining twin gestations by gestational age (completed week), chorionicity, and year of delivery. A 3:1 setting was chosen to achieve an 80% power at $P<0.05$ to detect a 10% inter-group difference in being small- or large- for gestational age (SGA and LGA, $>10^{th}$ percentile or $>90^{th}$ percentile, respectively). Gestational age was derived from the last menstrual period that was confirmed by first trimester ultrasound scans and from the day of oocyte retrieval in pregnancies after assisted reproduction. Chorionicity was established by standard ultrasonographic criteria performed by level III ultrasonographers, confirmed by careful examination of the delivered placenta by experienced obstetricians, and double-checked by pathologic examination of the placentas. Cases with pre-gestational diabetes were excluded from the analysis. Treatment was tailored according to blood glucose levels and given as in singleton pregnancies [1]. No elective preterm deliveries are done; however, indicated preterm deliveries were carried out, following corticosteroid treatment, on the basis of maternal and/or fetal conditions. In otherwise normally progressing gestations, we offered, after detailed counseling, elective deliveries at 36–37 completed weeks of gestation.

The following variables were considered in our analysis: maternal age and parity, pre-gravid body mass index (BMI, weight in kg/squared height in cm; BMI 25–30 was considered overweight, BMI>30 considered obese), mode of conception (spontaneous vs. iatrogenic), maternal complications, such as premature contractions (<34 weeks of gestation), hypertensive disorders (pre-eclampsia, pregnancy-induced hypertension, and chronic hypertension), preterm rupture of membranes (PTROM) at <34 weeks of gestation, mode of delivery, gestational age at birth, birth weight, frequency of being SGA and LGA (according to twin birth weight standards [2]), birth weight discordance of 25% (intertwin birth weight difference expressed as percentage of the heavier twin), frequency of Apgar scores <7 at 5 min, major malformations (excluding stillbirths), early (<7 days of life) neonatal death, and major neonatal morbidity (RDS diagnosed by clinical signs supported by classical X-ray findings, sepsis, intraventricular hemorrhage, retinopathy of prematurity, hyperbilirubinemia requiring either follow-up or phototherapy). We compared continuous data by using two-tailed Student's *t*-test, and categorical data by two-tailed Fisher's exact test. We used SPSS version 13 (Chicago, IL, USA) and True EPISTAT Software (Math Archives, Round Rock, TX, USA) for statistical analyses. P-values <0.05 were considered significant. The study has been approved by local institutional review board.

Results

The study group included 105 twin pregnancies with GDM (7.8% of the total number twin births). Table 1 shows the demographic data of twin gestations with GDM compared with 315 twin pregnancies without GDM matched for gestational age (mean 34.9 ± 2.1 weeks; 12.4% at 28–32 weeks, 26.7% at 33–35 weeks, and 60.9% at ≥36 weeks) and chorionicity (62.8% dichorionic twins).

Both groups were similar in terms of mean maternal age, frequency of maternal age >35 years, and parity but mothers of twins with GDM had a significantly greater pre-gravid BMI. As shown in Table 2, the greater pre-gravid BMI was a result of significantly more obese mothers of twins who eventually developed GDM. Although statistically insignificant, one cannot overlook the increased prevalence of hypertensive disorders and cholestasis of pregnancy among study group patients.

We further compared the proportion of pre-gravid normal BMI mothers who conceived spontaneously in both groups. This analysis showed that significantly fewer pre-gravid normal BMI mothers (n=34, 35.2%) had a spontaneous twin conception and eventually developed GDM compared with matched controls that did not (n=172, 54.6%; OR 0.4, 95% CI 0.3, 0.7).

Table 3 shows that twins born to mothers with GDM had a significantly increased prevalence of respiratory distress at birth and jaundice. These infants, however, had similar frequencies of major malformations, and similar birth weight characteristics. There was a single fetal death in the GDM group and three fetal deaths in the controls (one case of double death, with both twins having severe malformations), for an uncorrected (for malformation) stillbirth rate of 4.7:1000 twins in both groups. There were four neonatal

Table 1 Demographic data of twin gestations with GDM compared with matched for gestational age and chorionicity non-GDM controls.

	GDM n=105	Non-GDM n=315	Statistics
Mean maternal age (years)	31.4±4.8	30.5±5.2	NS
≥35 years	30 (28.5)	74 (23.5)	NS
Nulliparas	68 (64.8)	176 (55.9)	NS
Spontaneous pregnancies	70 (66.7)	241 (76.8)	NS
Mean BMI (kg/cm^2)	25.4±5.4	23.4±4.1	P<0.001
BMI <25 kg/cm^2 and spontaneous pregnancy	37 (35.2)	172 (54.6)	0.4 (0.3, 0.7)
Cesarean section	76 (72.4)	216 (68.6)	NS

Data presented as mean±SD or as n (%), statistics are shown as P-values or odds ratio (95% CI).
NS=not significant, GDM=gestational diabetes mellitus.

Table 2 Maternal complications during twin gestations with GDM compared with matched non-GDM controls.

	GDM n = 105	Non-GDM n = 315	Statistics
BMI 25–30 kg/cm^2	31 (29.5)	67 (21.3)	NS
BMI > 30 kg/cm^2	21 (20.0)	21 (6.7)	3.5 (1.7, 7.0)
Hypertensive disorders	29 (27.6)	58 (18.4)	NS
Preterm contractions	49 (46.7)	162 (51.4)	NS
Cholestasis of pregnancy	9 (8.6)	11 (3.5)	NS
PTROM	8 (7.6)	25 (7.9)	NS

Data presented as mean ± SD or as n (%); statistics are shown as P-values or odds ratio (95% CI).
NS = not significant, GDM = gestational diabetes mellitus, PTROM = preterm rupture of membranes.

mortalities: three in the GDM group (one infant with encephaloocele, one due to sepsis in an SGA infant born to a mother who had also pre-eclampsia, and one after PTROM of four weeks duration, born at 30 weeks) and one monochorionic twin in the non-GDM group who had congenital arthrogriposis. The uncorrected (for malformation) neonatal mortality rate was 14/1000 live births in the GDM group and 1.5/1000 in the controls, for an uncorrected perinatal mortality rate of 19/1000 and 6/1000, respectively.

Discussion

This is, to the best of our knowledge, the largest and most carefully matched case-control study on twin pregnancies complicated with GDM. A higher frequency of mothers who were obese before a twin-pregnancy required assisted reproduction and eventually developed GDM. This observation, albeit not surprising, may suggest a common denominator whereby obese women might require more frequent infertility treatment which, in turn, might result in more twin gestations, some of which complicated by GDM. The European Society of Human Reproduction and Embryology (ESHRE) Capri Workshop Group [3] maintained that obesity can affect reproduction through fat cell metabolism, steroids and secretion of proteins such as leptin and adiponectin and through changes induced at the level of important homeostatic factors such as pancreatic secretion of insulin, androgen synthesis by the ovary and sex hormone-binding globulin production by the liver. Hence the link between this obesity-related metabolic condition, infertility status [3, 10] and twin pregnancy is not surprising. It is also noteworthy that the possible association between the current recommendations on weight gain during early twin pregnancies and the potential of developing GDM has not been explored [5]. One may speculate that some borderline overweight women may turn obese due to increased calories intake during early twin pregnancy [4, 13].

Although expecting mothers of twins with GDM seem to fare as well (or as bad) as mothers without GDM, there was a definite trend towards more hypertensive disorders and cholestasis of pregnancy in the former group. It was somewhat unexpected that hypertensive disorders are not more frequent in twin as they are in singleton pregnancies affected by GDM. At this stage, and given the trend towards an increased risk of hypertensive disorders, we cannot exclude a type-II error. We also found an increased risk of respiratory distress in twins born to gestational diabetics and this complication was significant although the groups were *a priori*

Table 3 Fetal/neonatal complications in twin gestations with GDM compared with matched non-GDM controls.

	GDM n = 105	Non-GDM n = 315	Statistics
Mean birth weight (g)	2222 ± 452	2218 ± 432	NS
SGA	18 (8.6)	70 (11.1)	NS
LGA	8 (3.8)	11 (1.7)	NS
Discordant birth weight 25%*	8 (7.6)	33 (10.5)	NS
5-min Apgar score < 7	3 (1.4)	10 (1.6)	NS
Major malformations	7 (3.3)	15 (2.4)	NS
Respiratory distress	30 (14.3)	43 (7.0)	2.2 (1.3, 3.7)
Intraventricular hemorrhage	1	0	
Sepsis	4 (1.9)	7 (1.1)	NS
Retinopathy of prematurity	2	1	
Jaundice	22 (10.5)	12 (1.9)	6.0 (2.7, 13.2)
Fetal death	1 (0.5)	3 (0.5)	NS
Neonatal death	3 (1.4)	1 (0.2)	NS
Perinatal mortality	4 (1.9)	4 (0.6)	NS

*Data calculated per pregnancy.
Data presented as mean ± SD or as n (%), statistics are shown as P-values or odds ratio (95% CI).
NS = not significant, SGA = small for gestational age, LGA = large for gestational age, GDM = gestational diabetes mellitus.

matched by gestational age. Thus, our policy to recommend delivery at 36–37 weeks did not influence the rate of these complications and it seems that neonatal respiratory disorders appear to complicate twin pregnancies with GDM irrespective of gestational age.

The overall perinatal mortality rate in our cohorts suggests a three-fold increased uncorrected perinatal mortality (borderline significance) in the GDM group. However, it appears that most mortalities were related to fatal malformations and hence the corrected for malformation mortality rate seems to be low and similar in both groups.

Our data do not support the observation of Klein et al. [8] that twin pregnancies with insulin requiring gestational diabetes seem to have less birth discordance. However, this may be due to the different categorization of discrepant intertwin birth weight. Because we excluded patients with type I diabetes, we cannot comment on the observation of Tchobroutsky et al. [15] on a high-frequency of fetal malformation, but we could support the results of a small series evaluated by Keller et al. [7] who reported on a trend of greater likelihoods of RDS and hyperbilirubinemia among twins born to mothers with GDM.

Because one of the most significant causes of morbidity of multiple gestations is low birth weight, it was argued [6] that, at least theoretically, a ‘‘hidden’’ advantage might exist for twins born to women with GDM because the fetal growth-promoting effect of GDM may counterbalance the inherent growth restricting effect of the limited and overwhelmed uterine milieu in twin gestation. Surprisingly (or not), the data indicate no effect on birth weight parameters, although the frequency of LGA was almost twice higher. The best explanation for our observation is that the growth promoting effect of GDM is balanced by the growth inhibiting effect of the uterine constraints in twin gestations.

This study cannot address the role of adequate glycemic control in changing the outcomes of the mothers and their twins. Nor can this study address potential confounders of birth weight characteristics such as smoking, level of exercise, genetic predisposition for GDM, etc. Because our hospital is a referral center, we could not exclude an undetected bias if the women with GDM were more likely referred to our center for management whereas those without GDM more likely come from uncomplicated population of the Lisbon area.

Regardless, this study provides convincing data supporting the view that GDM is a further complication of an already complicated gestation.

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Prospective risk of intrauterine death of monochorionic-diamniotic twins

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Monochorionic twins
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Objective: The purpose of this study was to calculate the prospective risk of fetal death in monochorionic-diamniotic twins.
Study design: We evaluated 193 monochorionic diamniotic twin pregnancies that were followed and delivered after 24 weeks. Surveillance included cardiotocography and sonography performed at least once weekly. The prospective risk of fetal death was calculated as the total number of deaths at the beginning of the gestational period divided by the number of continuing pregnancies at or beyond that period.
Results: The fetal death rate was 5 of 193 pregnancies (2.6%; 95% CI, 1.1, 5.9); the prospective risk of stillbirth per pregnancy after 32 weeks of gestation was 1.2% (95% CI, 0.3% - 4.2%).
Conclusion: Under intensive surveillance, the prospective risk of fetal death in monochorionic-diamniotic pregnancies after 32 weeks of gestation is much lower than reported and does not support a policy of elective preterm delivery.

Monochorionic twins, comprising approximately 20% of all spontaneous twins and nearly 5% of iatrogenic twins,[1] are at a substantial higher risk of perinatal morbidity and death than their bichorionic counterparts.[2-4] This risk is attributed to the inherent pathologic condition that is associated with delayed zygotic splitting that leads to the increased prevalence of fetal and placental malformations. However, in monochorionic-diamniotic pregnancies, the precise cause of the high rate of adverse perinatal outcomes in pregnancies that are not complicated by congenital anomalies, twin-twin transfusion syndrome (TTTS), and/or growth restriction is not clear.

Evidently, not all monochorionic twin pregnancies are complicated a priori. A recent analysis of a large cohort of 455 monochorionic twins showed that 181 (39.8%) twin pairs were considered "uncomplicated" (ie, without signs of TTTS and exhibiting appropriate and concordant growth in each of the structurally normal twins).[5] This subset of "uncomplicated" monochorionic twins, however, was found to be at a considerable excess

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risk of intrauterine fetal demise (IUFD), despite being without apparent risk except of sharing a monochorionic placenta. The invariable presence of intertwin vascular connections in these placentas was suspected to be involved in some form of unexpected and acute TTTS. In that study,[5] the prospective risk of such unexpected IUFD after 32 weeks of gestation was 1 in 23 monochorionic-diamniotic pregnancies (4.3%; 95% CI, 1/11-1/63). With this risk in mind, one might question the wisdom of continuing the pregnancy of "uncomplicated" monochorionic twins after 32 weeks of gestation. In their commentary on this study, Cleary-Goldman and D'Alton[6] focused on the important dilemma that many practitioners are confronting increasingly often, namely the ideal gestational age at which to deliver apparently uncomplicated monochorionic twins. Whereas the results of the study of Barigye et al[5] seem to suggest that 32 weeks of gestation may be a reasonable date for elective preterm delivery to avoid unexpected IUFDs, the inherent risks of prematurity at that gestational age remain significant.[6]

In the absence of randomized studies, balancing the risk of elective preterm birth versus the risk of single or double IUFD is still challenging.[6] As a result, we carried out this retrospective cohort study to reassess the prospective risk of IUFD in our monochorionic twin population.

Material and methods

During the period September 1994 through March 2005, there were 893 twin pregnancies that were followed and delivered at the Maternity Dr Alfredo da Costa, Lisbon, Portugal, which is a tertiary perinatal center that cares for the Lisbon area and serves as a referral center for the south of Portugal. This figure represents approximately 1% of all deliveries. During this period, information about the pregnancy and delivery was registered prospectively on a preset form and subsequently entered into a computerized system. We excluded twin gestations that were delivered only and were not followed at our service.

For this study, we identified monochorionic twins. Monochorionicity was established by standard ultrasonographic criteria performed by level III ultrasonographers, confirmed by careful examination of the delivered placenta by experienced obstetricians, and double-checked by pathologic examination of the placentas. We restricted our analysis to twin births at >24 weeks of gestation.

Gestational age was derived from the last menstrual period that was confirmed by first trimester ultrasound scans and from the day of oocyte retrieval in pregnancies after assisted reproduction (ie, oocyte retrieval day minus 14). Prenatal diagnosis in the form of nuchal translucency thickness measurements, level III detailed anatomic scan, and genetic amniocentesis (when indicated) were performed in all cases. Our surveillance protocol in monochorionic twins included biweekly assessments between 24 and 30 completed weeks of gestation and weekly assessment thereafter. The prenatal care included nonstress testing of the 2 fetal heart rates and biophysical profile of both twins. Longitudinal growth assessment is performed biweekly. After 30 weeks of gestation, we performed Doppler analyses of the umbilical arteries supplemented with measurements of the peak systolic velocity in the middle cerebral artery, if signs of aberrant fetal growth were found. These measures were implemented during the study period as they became available in terms of equipment and experience. Subjects with either nonreassuring fetal findings or with maternal complications were submitted to daily to twice weekly maternal-fetal evaluations that were performed during hospitalization or during visits at an outpatient clinic setting. No elective preterm deliveries are done; however, indicated preterm deliveries were carried out on the basis of maternal and/or fetal conditions. Prophylactic antenatal corticosteroids (2 intramuscular doses of 12 mg betamethasone, 24 hours apart) were administered only if a preterm delivery was considered. In otherwise normally progressing gestations, we offered, after detailed counseling, elective deliveries at 36 to 37 completed weeks of gestation without lung maturity assessment.

The analysis was made per pregnancy or per fetus, as required. We excluded the stillborn fetuses from the analysis of birth weights and birth weight discordance because of the maceration that is associated with the prolonged interval between IUFD and delivery. The following variables were considered in our analysis: maternal age and parity, mode of conception (spontaneous vs iatrogenic), maternal complications such as premature contractions (<34 weeks of gestation), hypertensive disorders (preeclampsia, pregnancy-induced hypertension, and chronic hypertension), diabetes mellitus (gestational and pregestational), preterm rupture of membranes at <34 weeks of gestation, mode of delivery, gestational age at birth, birth weight, birth weight discordance of $>25\%$ (intertwin birth weight difference expressed as percentage of the heavier twin), frequency of TTTS, Apgar scores at 5 minutes (not available for 1 pair because of extreme prematurity), major malformations (excluding stillbirths), early (≤ 7 days of life) neonatal death, and major neonatal morbidity (respiratory complications, sepsis, and intraventricular hemorrhage).

Using the same method of "fetuses-at risk" that was employed by Barigye et al,[5] we derived the rate of fetal death in continuing pregnancies for each 2-week gestational period, starting at 24 weeks of gestation. This rate was calculated as the number of IUFDs that occurred within the 2 weeks after the beginning of the week divided by the number of continuing pregnancies

Table I Maternal and fetal/neonatal characteristics of 193 intensively monitored monochorionic diamniotic twin gestations that were delivered after 24 weeks of gestation

Characteristic	Measurement
Maternal age (y)	28.2 ± 4.8
Nulliparous women (n)	105 (54.4%)
Spontaneous conceptions (n)	183 (94.8%)
Pregnancy complications (n)*	
Premature contractions	79 (40.9%)
Hypertensive disorders	37 (19.2%)
Premature preterm rupture of membranes	13 (6.7%)
Diabetes mellitus	14 (7.3%)
Mode of delivery (n)	
Vaginal	63 (32.6%)
Cesarean birth in labor	26 (13.5%)
Elective cesarean	104 (53.9%)
Gestational age at delivery (wk)	34.8 ± 2.5
<32 (n)	18 (9.3%)
32-35 (n)	89 (46.1%)
≥36 (n)	86 (44.6%)
Birth weight (g)†	2156 ± 534
<1500 (n)†	43 (11.3%)
1500-2499 (n)†	230 (60.4%)
>2500 (n)†	108 (28.3%)
Birth weight discordance >25% (n)†	28 (14.5%)
Major malformations (n)†	16 (4.2%)
Twin-twin transfusion syndrome (n)	15 (7.8%)
IUFD (n)	
Per fetus	5 (1.3%)
Per pregnancy	5 (2.6%)
5-Minute Apgar score <7 (n)	5 (1.3%)
Early neonatal deaths (n)	7 (1.8%)
Major neonatal morbidity (n)*	
Respiratory	55 (14.4%)
Sepsis	7 (1.8%)
Intraventricular hemorrhage	2 (0.5%)

* Subjects may have >1 condition.
† Data excludes stillbirths.

at the beginning of that week. The prospective risk of IUFD was calculated as the total number of IUFDs at the beginning of the gestational period divided by the number of continuing pregnancies at or beyond that period.[5,7] Because few pregnancies continued beyond the 2-week period at ≥36 weeks of gestation, the prospective risk was not determined for this period. Our pediatricians followed the surviving infant in cases with single IUFD, and their condition was recorded in our database. We derived the binomial distribution 95% CI for rates with standard statistical formulas.

The study has been approved by local institutional review board.

Results

We identified 193 monochorionic diamniotic sets among the 893 twins who were followed and delivered during the study period (21.6%). None of the sets were excluded from the analysis; the characteristics of this monochorionic-diamniotic twin cohort are shown in Table I. In our cohort, 107 pregnancies (approximately 55% of all cases) were delivered at <36 weeks of gestation; 39 pregnancies (36.4%) had a spontaneous preterm labor, and in 68 cases we delivered the pregnancy prematurely because of fetal indication (63/68; 92.6%) or maternal indications (5/68; 7.4%). The IUFD rates were 5 of 193 pregnancies (2.6%; 95% CI, 1.1, 5.9) and 5 of 86 fetuses (1.3%; 95% CI, 0.5, 3.0).

Major fetal malformations included 2 concordant chromosomal anomalies (inversion of chromosome 3, also present in the mother), 9 congenital heart anomalies, 2 kidney anomalies, and 1 omphalocele. All IUFDs occurred in the nonpresenting twin (ie, in twin B). Four of the 5 IUFDs occurred remote from term (Table II) and were delivered with their apparently normal co-twin at an interval of 3 to 7 weeks. Because of severe maceration, autopsies were unreliable in terms of anomaly detection; however, all these pregnancies were under close observation because of early onset severe discordant growth (>25% as estimated from the last sonography), but without signs of TTTS. The fifth IUFD occurred at 34 weeks of gestation in a fetus with a nonreassuring fetal heart rate tracing in a pregnancy that was complicated with severe preeclampsia. IUFD occurred just before the planned cesarean delivery, and the stillborn fetus weighed 1780 g (19% discordant). Because no other cause was found, this potentially avoidable death was presumably related to acute fetal distress. All but 1 of the survivors are developing normally at a follow-up of at least 3 years. One survivor, however, has cerebral palsy. This child lost its co-twin at 25 weeks of gestation, was growing normally, was delivered by elective cesarean 7 weeks later, and had a 5-minute Apgar score of 10. This event occurred before we implemented antepartum level III ultrasound scans and serial magnetic resonance imaging of the surviving single twin. Thus, we are unable to exclude the possibility that brain lesions could have been detected before birth in this case.

Four of the 7 early neonatal deaths were a result of a congenital heart anomaly (including 1 pair with a concordant cardiac anomaly): One death was the result of a traumatic forceps delivery of a 31 weeks of gestation (1545 g, second twin); 1 death was the result of sepsis at 33 weeks of gestation in a 1845-g infant; and one death was the lighter twin who weighed 695 g from a pregnancy that was complicated by TTTS and underwent spontaneous preterm delivery at 29 weeks of gestation. The uncorrected perinatal (stillbirth plus early neonatal) mortality rate of this cohort was 12 of 381 infants (3.1%) or 31.5 of 1000 live born infants. The uncorrected for anomalies early neonatal mortality rate was 7 of 381 infants (1.8%, 18.3 of 1000 live born infants), and the corrected for

Table II Rate and prospective risk of unexpected fetal demise in 193 intensively monitored monochorionic-diamniotic twin gestations that were delivered after 24 weeks of gestation

	Continuing (n)		Deaths per period (n)		IUFD rate per period (n/N)		Deaths in continuing (n)		Prospective risk of IUFD (n/N)*	
Gestational age (wk)	Pregnancies	Fetuses	Per pregnancy	Per fetus	Per pregnancy	Per fetus	Pregnancies	Fetuses	Per pregnancy	Per fetus
24-25	193	386	2	2	2/193 (1/97)	2/386 (1/193)	5	5	5/193 (1/37), 2.6%, [1.1,5.9]	5/386 (1/77), 1.3%, [0.5, 3.0]
26-27	193	384	1	1	1/193	1/384	5	5	5/193 (1/37), 2.6%, [1.1,5.9]	5/384 (1/77), 1.3%, [0.5, 3.0]
28-29	191	379	0	0	0/191	0/379	4	4	4/191 (1/48), 2.1%, [0.8, 5.2]	4/379 (1/95), 1.0%, [0.4, 2.7]
30-31	183	363	1	1	1/183	1/363	4	4	4/183 (1/46) 2.2% [0.9, 5.5]	4/363 (1/91) 1.1% [0.4, 2.8]
32-33	168	332	0	0	0/168	0/332	2	2	2/168 (1/84), 1.2%, [0.3, 4.2]	2/332 (1/166), 0.6%, [0.1, 2.2]
34-35	140	276	1	1	1/140	1/276	1	1	1/140, 0.7%, [0.1, 3.9]	1/276, 0.4%, [0.06, 2.0]
≥36	88	171	0	0	0/88	0/171	0	0		

* 95% CI is given in brackets.

anomalies early neonatal mortality rate was 3 of 381 (0.8%, 7.9 of 1000 live born infants).

Comment

Elective preterm delivery of presumably "uncomplicated" pregnancies is reserved for cases in which evidence shows that continuing the pregnancy undoubtedly may increase the risk for the fetus(es) and that this potential risk outweighs the risks that are associated with preterm birth. Such a "ticking bomb" situation that warrants intensive antenatal care and elective preterm delivery has been described for monoamniotic twin pregnancies in which cord entanglement with a potential to become dangerously tightened is almost invariably seen.[8,9] However, the extension of this approach to all diamniotic-monochorionic twins,[10] including those who are apparently "uncomplicated," has been suggested only recently in the seminal study that was conducted by Barigye et al.[5] In this study, the authors reiterated the well-known association of monochorionicity and the risk for an unexpected single or double fetal death past 32 weeks of gestation. Single fetal death is of special importance because, as opposed to dichorionic twins, intertwin agonal transfusion results in up to a 38% risk of death and a 46% risk of neurologic damage to the co-twin.[10] The authors concluded that the significant prospective risk merits further studies that will examine the potential salvage of these IUFDs by elective preterm delivery.

Our study, although inspired by that of Barigye et al,[5] is different in 2 main aspects. First, their seminal study was comprised of presumably "uncomplicated" cases, whereas our study did not exclude malformations, growth problems, and TTTS. This difference was expected to increase the prospective risk of IUFD in our cohort. However, our results show a much lower prospective risk per pregnancy and per fetus in each stratum of gestational ages (Table II) compared with the risks reported by Barigye et al.[5] Importantly, the prospective risk of antepartum stillbirth after 32 weeks of gestation was 4.3% (95% CI, 1.6% - 9.1%) as compared with 1.2% (95% CI, 0.3% - 4.2%) in our series. Thus, according to our data, 1 case of IUFD would be prevented for every 84 monochorionic pregnancies that are delivered at 32 weeks of gestation and 1 case of IUFD for every 140 pregnancies at 34 weeks of gestation, compared with 23 and 30 pregnancies in the series of Barigye et al.[5]

The second main difference between our study and that of Barigye et al[5] is the more intensive antenatal surveillance that is used in our service in terms of frequency (weekly vs biweekly) and methods (cardiotocography and sonography vs sonography alone). We acknowledge that there are no data to support the frequency of antenatal testing in uncomplicated twins and that these are scheduled empirically rather than according to evidence-based recommendations. However, because all IUFDs occurred between 1 and 2 weeks after the last scan in the study of Barigye et al,[5] it is likely that more frequent assessments of fetal well-being may reduce, at least in part, the prospective risk of IUFD. In our cohort, nearly 55% of the pregnancies were delivered preterm as a result of our surveillance protocol; in the majority of pregnancies, the preterm delivery was for fetal indications. Nevertheless, it is unknown and probably can never be known how many unanticipated fetal deaths have been avoided by our antenatal surveillance protocol.

Increasing the frequency of antenatal assessments and implementing more sophisticated surveillance methods are undeniably more expensive. However, if the alternative to intensive antenatal assessments is elective preterm delivery, the cost of a prolonged stay in the neonatal intensive care unit as a result of iatrogenic prematurity should certainly be added to the equation and conceivably would offset the costs that are involved in intensive monitoring.

The American College of Obstetricians and Gynecologists, in its most recent practice bulletin on complicated twin and other multiple gestations[11] did not differentiate between the risk of dichorionic and monochorionic twins and therefore did not describe specifically the necessary fetal well-being assessment of monochorionic twins nor the possibility of elective preterm birth. However, as Cleary-Goldman and D'Alton[6] pointed out, some maternal-fetal medicine centers in the United States are conducting antenatal surveillance more frequently than once every 2 weeks and are using cardiotocography in addition to ultrasound and Doppler studies.

Another pertinent question is the timing of elective preterm delivery for twins. Most clinicians would probably agree that 32 weeks of gestation is too early. Similarly, many clinicians would agree that 37 to 38 weeks of gestation is the optimal gestational age for twins.[12] One possible concession is to offer delivery of these apparently uncomplicated monochorionic twins at approximately 34 to 35 weeks of gestation after antenatal corticosteroid administration and appropriate counseling regarding the pros and cons of expectant management versus elective preterm delivery.[6] Based on our results and on recent observations regarding the excess risk of respiratory complications after near term twin delivery,[13,14] we believe that our policy of offering elective preterm birth after 36 completed weeks of gestation is a more reasonable compromise.

The differences between our study and that of Barigye et al[5] may relate to difference in the referral populations. Although the 2 maternal-fetal medicine services are considered tertiary and although the prevalence of fetal malformation in our series (4.2%; Table I) was similar to that reported by Barigye et al[5] (27/480; 5.6%), we had only approximately 8% TTTS cases (Table I), whereas Barigye et al excluded 164 of 480 cases (34.2%) of TTTS from the analysis. Our low TTTS prevalence is because many patients (data not available) opted for induced late abortion rather than continuation of pregnancy after 24 weeks of gestation. Given the strict criteria that were used by Barigye et al, the nearly twice higher than the accepted 15% to 20% prevalence of TTTS may suggest that a different referral policy may account for the higher intrauterine death. Because of the long interval between fetal death and delivery, we were unable to reproduce the pathologic observation that suggests that death occurred because of some form of acute TTTS.[5]

Finally, IUFDs among dichorionic twins does also exist. However, this risk is considerably higher in monochorionic twins[4,15] and highlights the special attention that is required for monochorionicity, which should translate into more intensive antenatal assessments. However, the prospective risk of IUFD that was found in our study does not indicate preterm elective delivery of monochorionic twins.

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Induction of labor with oral misoprostol in nulliparous mothers of twins

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Abstract

The efficacy and safety of oral misoprostol for labor induction of twins is unknown. We conducted a retrospective case-control study to evaluate the use of oral misoprostol in near term (≥35 weeks) twin pregnancies in nulliparas. Eligible cases were given 100 mcg oral misoprostol, which was repeated after 6 h if labor did not start. Either a third dose or diluted oxytocin infusion were given in intractable cases. Diluted oxytocin infusion was used for augmentation. Controls were nulliparas delivered at ≥35 weeks by elective cesarean section. The two groups were comparable in most aspects, except for fetal malpresentation, which was the major reason for avoiding induction. Of the 69 patients in whom labor was induced, 53 (76.8%) had a vaginal birth, 3 (4.3%) had a combined twin delivery, and 13 (18.8%) had a cesarean during labor. The mean length of stay of the neonates was significantly shorter among study cases, without significant difference in the frequency of delayed discharges as an overall proxy for neonatal complications. Labor induction with oral misoprostol could be offered to patients in whom near term vaginal twin delivery is unequivocally permitted and wish to deliver by the vaginal route.

Keywords: Cesarean section; labor induction; misoprostol; twins.

Introduction

Cesarean birth and labor induction for twin pregnancies increased substantially in the United States during the last decade, and these changes in obstetrical practice have been associated with a significant decline in the rate of stillborn twins [1]. This conclusion comes from a recent retrospective cohort study of more than a million twin live births and stillbirths in the United States between 1989 and 1999, showing that the rates of labor induction and cesarean birth among twin live births increased by 138% (from 5.8 to 13.8%) and 15% (from 48.3 to 55.6%), respectively [1]. During the same period, there was a 43% decline in the stillbirth rate (from 24.4 to 13.9 per 1000 fetuses at risk). Importantly, the decline in the rate of twin stillbirths was larger at later gestational ages where the largest absolute increases in labor induction rates were observed [5]. These observations confirmed data from France and Australia, indicating that decisions to minimize fetal deaths in twin pregnancies increased preterm deliveries, and thus, lower rates of stillbirths are achieved seemingly at the price of delivering more twin infants before term [14, 15].

Further analysis of the American database suggests that in 1999 more than 15,000 live born twins were registered as being delivered after labor induction [6]. Regardless, these epidemiological studies [5, 6, 14, 15] did not consider the method of labor induction, method-related complications, or the frequency of failed inductions. At the same time the ACOG Practice Bulletin [2] included the multifetal pregnancy among obstetric circumstances that “are not contraindications to the induction of labor but do necessitate special attention”. Regrettably, this Practice Bulletin remained silent about the method of induction as well as the special attention that is required, whereas a more recent Practice Bulletin on multiple gestations [3] did not even mention the issue of labor induction in twins.

The clinical concern about labor induction in advanced twin gestations is based on the potential hyperstimulation of an overdistended uterus. This concern is represented by a paucity of published studies related to labor induction in twin gestations. These few and small-sized studies suggested that oxytocin stimulation [9, 10], intrauterine balloon [12], or even prostaglandin E2 [19] were effective and safe for cervical ripening in the process of labor induction in twin gestations.

Over the past 15 years, data have been accumulated regarding the safety and efficacy of misoprostol (Cytotec, Searle), a prostaglandin E1 analogue, as a method for cervical ripening and labor induction [4]. More recently, stepwise oral misoprostol appears to be as effective as vaginal misoprostol for cervical ripening with a low inci-

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dence of uterine hyperstimulation, no increase in side effects, a high rate of patient satisfaction, and a lower cesarean section rate [20]. The ACOG Committee Opinion on labor induction with misoprostol, which published favorable comments related to this method of induction, also remained silent about its potential application in twin gestations [1].

Based on our experience with this drug in singletons, we performed this retrospective case-control study to evaluate the use of misoprostol in near term twin pregnancies.

Material and methods

During the period September 1994–December 2004, there were 825 twin pregnancies followed and delivered at our maternity center. This figure represents 0.98% of all births. Twin pregnancies that were delivered immediately upon admission were not included in the study. During this period, information about the pregnancy and delivery was prospectively registered on a preset form and subsequently entered into a computerized system. Because the purpose of this study was to evaluate the efficacy and safety of near term labor induction in twins using oral misoprostol, and in order to avoid the confounding effect of parity, we restricted this study to nulliparous women. Hence, the study group comprised nulliparous patients delivered following oral misoprostol induction at ≥35 weeks' gestation. Because we were interested in outcome related to the induction process and to avoid the confounding effect of spontaneous birth, the control group comprised nulliparous patients delivered at ≥35 weeks' gestation by elective cesarean section.

Induction of labor was not done in patients with previous uterine surgery, an abnormal (non-vertex) presentation of the first twin, when the patient opted for an elective cesarean section, or when a vaginal delivery was contraindicated. Eligible patients for induction by misoprostol had a closed and uneffaced cervix with intact membranes. Following a detailed informed consent process, a comprehensive maternal and fetal assessment (dual fetal heart rate tracing, biophysical profile, and estimated fetal weight) to exclude cases from the induction process, oral misoprostol was given in a dose of 100 μg, which was repeated after 6 h if there were no contractions or cervical dilatation. If the second dose did not induce labor, either a third dose is given or diluted oxytocin infusion (starting with 5 and increasing up to 15 mU/min) is initiated. Cases that were successfully induced by misoprostol alone and misoprostol and oxytocin comprised the study group. Augmentation of labor was done, if necessary, by diluted oxytocin infusion. We considered an induction successful if the patient delivered by the vaginal route. Failed induction was considered if intrapartum cesarean section was performed. During labor, we rupture the membranes at a relatively early stage in order to have access for direct fetal heart rate monitoring of the presenting twin (enabling accurate dual monitoring, performed almost invariably) and to reduce uterine overdistension.

The following variables were considered for analysis: maternal age, mode of conception (spontaneous or by assisted reproduction), maternal complications during pregnancy (premature contractions and hypertensive disorders), maternal complications that indicate delivery near term (≥36 weeks, including semi-indications such as worsening dyspnea, sleeplessness, severe depending edema, etc. [3]), fetal indications (such as growth aberration or oligohydramnios in one or both gestational sacs); fetal presentation (vertex–vertex or other), and frequency of monochorionic twins. We evaluated the induction method by the length of the active phase of labor (from 3 cm of dilatation to delivery) and by the need for intrapartum cesarean delivery in the study group. Postpartum hemorrhage and infectious morbidity in both study and control groups were considered as method complications. Neonatal outcomes included birth weights, 5-min Apgar scores of <7, trauma, admission to and length of stay at the neonatal intensive care unit. The overall outcome was evaluated by the frequency of delayed discharge of the infants as a result of neonatal complications (such as respiratory distress, and need for mechanical ventilation, hyperbilirubinemia, and infection). Umbilical cord blood gases were not evaluated.

The data were evaluated using the Microsoft Excel® program (Microsoft Corporation, Redmond, Washington). We used the True EPISTAT Software (Math Archives, Round Rock, TX) to compare the induction and the elective cesarean section cases. We performed Student's *t* and chi-square tests for continuous and categorical variables, respectively. We derived the odds ratios and 95% confidence interval, as well as P values (considered significant if <0.05). The local Ethical Committee approved the study.

Results

During the study period, 69 patients (8.3% of the entire cohort) met the inclusion criteria for labor induction with oral misoprostol near term. The eligible control group comprised 116 (14.1%) patients. Table 1 shows the comparison of maternal and fetal characteristics between the groups. Study patients were slightly younger and comprised slightly more (borderline significance) spontaneous conceptions, but have the same frequency of pregnancy complications, mean gestational age, similar frequencies for the indication leading to induction of labor, and similar frequencies of monochorionic twins. There was a much higher frequency of vertex-vertex combination of presentations among the study group. Taken together, Table 1 suggests that the two groups were comparable in most aspects, except for fetal malpresentation, which was the major reason for avoiding inductions in these patients.

Of the 69 patients in whom labor was induced, 53 (76.8%) had a vaginal twin birth, 3 (4.3%) had a combined twin delivery (i.e., cesarean section for the second twin), and 13 (18.8%) had a cesarean delivery during labor. Combined twin delivery was done because of difficult delivery of a malpresenting twin (n=1) and intrapartum signs of fetal distress in the second twin (n=2). The indications for cesarean section during labor were arrest disorders of the active phase (n=10) and suspected fetal distress in the remaining 3 cases.

The mean duration of labor from the beginning of the active phase until delivery in the successful induction cases was 225±153 min. This was achieved in 41 cases (59.4%) with misoprostol only, and in the remaining cas-

Table 1 Comparison between the clinical presentation of the labor induction and elective cesarean section groups. Data shown as N (%) or as mean ± SD. Statistics are shown as P values for continuous data, and by odds ratio (95% confidence interval) for categorical data.

	Labor induction	Elective cesarean section	Statistics
N	69	116	
Maternal age (yrs)	28.5 ± 5.4	29.3 ± 6.6	P < 0.01
Spontaneous pregnancies	49 (75.4)	63 (54.7)	2.1 (1.04,4.1)
Pregnancy complications			
Preterm contractions	29 (42.0)	50 (43.1)	1.0 (0.5, 1.8)
Hypertensive disorders	13 (18.8)	32 (27.5)	0.6 (0.3, 1.3)
Gestational age (d)	256.0 ± 6.0	254.8 ± 7.0	P = 0.27
Indication for induction*			
Semi-indications at ≥36 weeks	46 (66.6)	91 (78.4)	0.5 (0.3, 1.1)
Maternal	14 (20.3)	28 (24.1)	0.8 (0.4, 1.8)
Fetal	8 (11.6)	20 (17.2)	0.6 (0.2, 1.6)
Stillbirth	0	3 (1.3%)	
Vertex-Vertex	56 (81.1)	28 (24.1)	13.5 (6.1, 30.5)
Monochorionic	16 (23.1)	18 (15.5)	1.6 (0.7, 3.7)

*Only major indications were considered for the analysis. Some patients may have more than one indication.

es with the addition of oxytocin induction. There were no cases of uterine hyperstimulation or uterine rupture in the study group. One case of postpartum hemorrhage and one case of postpartum infection complicated the elective cesarean group. One case of failed induction was subsequently re-operated to drain an abdominal incision hematoma.

The comparison of fetal outcome variables is shown in Table 2. There was a significantly higher birth weight of the firstborn twin (but not of the second born) in the study group. Admission to the neonatal intensive care unit was required for one infant in each group, and this was indicated for neonatal respiratory difficulties. The mean length of stay of the neonates at the hospital was significantly shorter among the study cases, although there was no significant difference in the frequency of delayed discharges as an overall proxy for neonatal complications.

Discussion

Every method for labor induction should be evaluated by its safety and efficacy. To the best of our knowledge, this is the first study discussing the use of oral misoprostol to induce labor in twins, and hence, there are no other published studies to compare with. For this reason, we limit our discussion to the use of oral misoprostol in singletons and to other methods of labor induction in twins.

Misoprostol is an inexpensive prostaglandin E1 analogue administered orally or vaginally, easily stored, and known to have few systemic side effects when compared to placebo, vaginal or intracervical prostaglandin E_2, and oxytocin [11]. In terms of safety, it was suggested that effective oral regimens may have an unacceptably high incidence of complications such as uterine hyperstimulation and possibly uterine rupture [4, 20], a concern that is not shared by recent studies comparing oral misoprostol to other labor induction regimens in singletons [8, 11, 13, 17]. In our present series of twin pregnancies, labor induction with oral misoprostol appears to be safe, for both mother and twins. This is of special importance since we used a seemingly higher dose of misoprostol as recommended in the literature for singleton births [1]. Moreover, in a series of 69 labor inductions in multiparas with twins managed in our hospital, no uterine hyperstimulation was encountered (data not shown).

In terms of efficacy, our results show that induction was successful in 80% of the cases eligible for induction, and in 60% of these cases (about 50% of all inductions),

Table 2 Comparison between neonatal outcomes of the labor induction and elective cesarean section groups. Data shown as N (%) or as mean ± SD. Statistics are shown as P values for continuous data, and by odds ratio (95% confidence interval) for categorical data.

	Labor induction	Elective cesarean section	Statistics
Birth weight			
Twin A	2551 ± 315	2450 ± 282	P = 0.02
Twin B	2432 ± 320	2354 ± 482	P = 0.1
5-min Apgar < 7	0	2 (0.9%)	
Length of stay (d)	4.0 ± 2.3	5.2 ± 3.0	P < 0.01
Delayed discharge	10 (7.2%)	22 (9.5)	0.8 (0.3,1.9)

labor was induced with misoprostol alone. These success rates are comparable to those reported in singletons [8, 17]. In addition, fetal outcomes were entirely comparable between the labor induction and the elective cesarean groups, and associated with an overall reduction of neonatal hospitalization (Table 2). Finally, in our series of successful inductions, vaginal birth was achieved (from the beginning of the active phase) within 225 ± 153 min, in agreement with the results of Schiff et al. [16] who found that twin gestations have a significantly shorter first stage of labor than do singleton gestations, and in contrast to the data provided by Silver et al. [18] who found that the active phase dilation in twins proceeds at a slower rate than that observed in singleton pregnancies.

Other methods exist for labor induction in twins. For example, Manor et al. [12] evaluated the efficacy and safety of labor induction using an intrauterine balloon catheter in twin pregnancies. In the series of 17 cases, vaginal delivery was achieved in 15 (88.2%) patients and all neonates had a perfect 5-min Apgar score. Suzuki et al. [19] induced labor in 17 twin gestations with oral prostaglandin E_2, and did not report any particular side effects. However, most reports in the literature probably used artificial rupture of membranes and oxytocin stimulation as a method of induction [10].

It is evident that not all twin pregnancies are candidates for labor induction, and from our study it appears that the obstetrical decision for an elective cesarean section was primarily related to fetal malpresentation, i.e., a combination other than vertex-vertex (Table 1). It also seems that both patients and their caregivers are more reluctant to choose labor induction in non-spontaneous twin gestations (Table 1). This trend, namely, cesarean section for “premium” twin pregnancies, is quite reasonable given the impact of the history of subfertility on decision making during labor and delivery [7]. As it appears, labor induction could be offered to patients in whom near term vaginal twin delivery is unequivocally permitted and to those who prefer the vaginal to the abdominal route.

Regardless of the favorable outcome associated with labor induction in our series of nulliparas with twins, we acknowledge the fact that such a procedure needs a dedicated obstetrical team and close observation throughout the induction process as well as during labor and delivery. Obviously, larger series are needed to exclude the possibility of rare events associated with labor induction such as uterine rupture.

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Puerperal complications following elective cesarean sections for twin pregnancies

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Abstract

Objective: To estimate the maternal puerperal morbidity in elective and emergent cesareans in twins.
Study design: We evaluated postpartum complications among patients who underwent elective cesarean birth for twin pregnancy. This group was compared to matched singletons and to emergent cesareans in twins.
Results: During the period September 1994–March 2006 there were 299 (47.4%) elective and 80 (12.7%) emergent cesarean sections in twin pregnancies, for a total of 379 (60.1%) cesarean births for both twins. Controls included 299 cases of elective cesareans in singletons. The comparison between elective and emergent cesareans and between elective cesareans in twins and in singletons found no significant differences in postpartum fever, scar infection, and postpartum hemorrhage. Venous thromboembolism occurred in two twin pregnancies, one in the elective and one in the emergent cesarean group. Postpartum hysterectomy was required in a singleton pregnancy following an elective cesarean birth.
Conclusion: At present, no data exist to show a disadvantage for a planned cesarean birth for twins.

Keywords: Cesarean; postpartum; puerperal morbidity; singletons; twins.

Introduction

Current efforts to diminish the escalating numbers of multiple pregnancies effectively reduced the incidence of higher-order multiples [4, 9]. At the same time, however, the number of twins is still increasing. The most recent USA data indicate that twin birth rate increased 2% in 2004, to 32.3 twins per 1000 births, another all-time record high. The twinning rate has increased 42% since 1990 and 70% since 1980. The most recent available national data from the USA indicate that as many as 132,219 twin births occurred in 2004 [6]. A similar trend has been observed in the United Kingdom as well as in other developed countries [4, 9]

As the numbers of twins increase, the mode of delivery becomes more pertinent. The United States cesarean birth rates increased 13% (from 51.9 to 55.0%, 95% CI 12–14) between 1989–1991 and 1997–1999 among twins delivered at ≥22 weeks and weighing ≥500 g [2]. Although this rate does not include the period after the publication of the Term Breech Trial [5], it represents an average increase of 52, 28 and 9% among twin pregnancies delivered at 22–27 weeks', 28–33 weeks' and at ≥34 weeks' gestation, respectively. It was rightfully noted that the rates increased to a greater extent at earlier rather than at later gestational ages, but the absolute number of cesareans was much higher at later gestational ages [2]. These figures are quite similar to the commonly cited rates of 50–60% abdominal births among twins and nearly 100% among triplets [3]. In the UK, the 2001 cesarean rate for twin deliveries was 59% [8].

At present, many of the circumstances that may have led to a twin pregnancy are commonly used as an indication for an elective cesarean delivery of twins. It appears that patients, as well as their attending clinicians, may base their decision for a cesarean in such "premium" pregnancies, intentionally or not, on quantitative arguments that are difficult to interpret and on qualitative variables that are impossible to quantify [3].

These considerations are contrasted with surprisingly scant information about puerperal morbidity following a planned compared to an emergent cesarean birth for twins, and compared with cesareans in singletons [1, 10]. Such information might be an important argument in the continuing discussion about the preferred mode of delivery of twins. The purpose of this paper was to estimate the maternal puerperal morbidity in elective and emergent cesareans in twins.

Materials and methods

During the period September 1994–March 2006, there were 946 twin pregnancies followed and delivered at the Maternity Dr. Alfredo da Costa, Lisbon, Portugal. This figure represents

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nearly 1% of all deliveries. During this period, information about the pregnancy and delivery was prospectively registered on a preset form and subsequently entered into a computerized system. This study focused on patients delivered by elective cesarean section as compared with emergent cesareans (defined as a decision taken during trial of labor for both twins). Thus, cases of cesareans for the second twin only—the so-called "combined twin delivery"—were excluded from the analysis. In addition, we focused on deliveries at ≥32 weeks, to avoid the confounding effects of indications for very preterm cesareans. Finally, all cases with premature rupture of membranes, irrespective of the *a priori* planned mode of delivery, were counted as emergency cesareans.

For a secondary comparison, we created a new dataset of a matched cohort of singletons, comprising the successive singleton pregnancy that had a planned, elective, cesarean birth performed at ≥32 weeks. Obviously, the indication for elective cesarean deliveries in twins and singleton differed. However, these indications are not associated with increased risk of puerperal morbidity that comprises the study variables listed below. The matching process assumes that the consecutive planned cesarean delivery in singletons within the same gestational age limits is the best randomly selected matched control for every case of elective cesarean in twins.

The following variables were compared: maternal age, parity, mode of conception, gestational age at birth, and birth weight. The study variables of interest were postpartum fever (defined as >38°C, measured twice, at 24 h postpartum or later), scar infection (defined as evident infection occurring during hospitalization, requiring either of the following measures: drainage, exploration of the scar, and antibiotic therapy), postpartum hemorrhage (defined as the need for blood transfusion or for active intervention to stop bleeding), and venous thromboembolism.

Our intraoperative protocol of antibiotic therapy (2 g of cephazoline, or an equivalent for allergic patients) was given following clamping of the singleton and the second twin's umbilical cord. Similarly, and irrespective of plurality, all cases received the same protocol of dilute oxytocin infusion. All cesareans were performed by senior staff. As noted above, in our service, rupture of membranes occurring in a patient scheduled for an elective cesarean changes her status to an emergent case.

The data were evaluated using the Microsoft Excel® program (Microsoft Corporation, Redmond, Washington). Comparisons were made between maternal variables of the three groups, but gestational age and birth weight variables were done between the twin groups only. We used the True epistat Software (Math Archives, Round Rock, TX) to perform Student's *t* and Fisher's exact tests to compare continuous and categorical variables, respectively. We derived P-values (considered significant if <0.05) and odds ratios (OR) and 95% confidence interval (CI) for these comparisons. The study was approved by the local Ethical Committee.

Results

During the study period, there were 631 women delivered at ≥32 weeks, including 299 (47.4%) elective and 80 (12.7%) emergent cesarean sections in twin pregnancies, for a total of 379 (60.1%) cesarean births for both twins. We excluded 15 (2.4%) cases of combined twin delivery for a total of 237 (37.5%) vaginal births for both twins. Controls included 299 cases of elective cesareans in singletons.

Table 1 shows the comparison between the study and control groups. The mean maternal age in the three groups was similar; however, mothers who had an elective cesarean in singletons were more frequently over 35 years. Nulliparas were more frequent in twins compared to singletons and, as expected, there was a significantly lower frequency of spontaneous conceptions among twins compared to singletons. No difference was found in the comparison of the neonatal characteristics within the twin groups.

The comparison of the postpartum complications (Table 2) showed no significant difference between elective and emergent cesareans in twins and between elective cesareans in twins and singletons. Despite the insignificant differences it seems that elective cesareans

Table 1 Maternal and neonatal outcomes. Data presented as mean±SD or as n (%).

	Twins		Singletons
	Elective cesareans	Emergent cesareans	Elective cesareans
n	299	80	299
Maternal age (years)	30.9±5.1	29.8±5.3	31.3±6.3
Age>35[¶]	51 (17.0)	10 (12.5)	95 (31.8)
Nulliparas[§]	158 (52.8)	47 (58.7)	82 (27.4)
Spontaneous pregnancies*	231 (77.2)	68 (85.0)	289 (96.6)
Gestational age (weeks)	35.9±1.4	35.8±1.6	38.6±2.4
<35 weeks	52 (17.3)	18 (22.5)	18 (6.0)
Total birth weight (g)	4799±726	4807±751	3239±750
<1500 g	14/598 (2.3)	3/160 (1.9)	10/299 (3.3)
<2500 g	346/598 (57.8)	91 (56.9)	35/299 (11.7)

¶Twins vs. singletons OR 0.4 (95% CI 0.3, 0.7).
§Twins vs. singletons OR 3.0 (95% CI 2.1, 4.2).
*Twins vs. singletons OR 0.1 (95% CI 0.05, 0.2).

Table 2 Puerperal complications. Data are shown as n (%), statistics are shown as OR (95% CI).

	Twins	Singletons	Statistics
Postpartum fever			
Elective	7 (2.3)	6 (2.0)	1.2 (0.3, 4.0)
Emergent	5 (6.3)		
Statistics	0.3 (0.1, 1.3)		
Scar infection			
Elective	6 (2.0)	2 (0.7)	3.0 (0.5, 14.1)
Emergent	4 (5.0)		
Statistics	0.4 (0.1, 1.7)		
Postpartum hemorrhage			
Elective	11 (3.7)	3 (1.0)	3.8 (0.9, 12.5)
Emergent	3 (3.8)		
Statistics	1.0 (0.2, 3.6)		

in twins have a lower incidence of postpartum fever and scar infection compared to emergency cesareans in twins or elective cesareans in singletons. Postpartum venous thromboembolism occurred in two twin pregnancies, one in the elective and one in the emergent cesarean group. Of note is that postpartum hysterectomy was required in one case of hemorrhage in a singleton pregnancy following an elective cesarean birth.

Discussion

A recent analysis of epidemiological data by Meyer [7] found that 97 cesarean sections would be required to prevent a serious morbidity or mortality in a second twin. This number was within the range needed to prevent uterine rupture during a trial of labor following a cesarean (1:556) or morbidity related to vaginal breech delivery (1:167). Meyer rightfully pointed out that the current balance of risks related to cesarean birth in twins is incomplete because the potential risk of cesarean birth is practically unknown. Indeed, post-cesarean maternal complications are relatively rare and potentially underreported in epidemiological datasets.

Bearing in mind the potential type II (beta) error in the statistical analysis of data from a single center and from a relatively short period of observation, we used a carefully selected matched cohort that found that the complication rates among elective cesareans in twins were similar to those in emergent cesareans in twins and in elective cesareans in singletons. At the same time, however, a trend could be seen, whereby the frequencies of complications were 2–4 times higher in twins than in singletons (Table 2).

Our data are unable to confirm the origin of postpartum fever reported by Suonio and Huttunen [10] who evaluated the infectious complications of 122 consecutive cesarean twin births in Finland. These authors found that the incidence of endometritis and wound infection were nearly thrice and twice higher in twins compared with singleton cesarean deliveries, respectively. The authors identified young maternal age (<25 years) and a prolonged interval between PROM and delivery (>6 h) as risk factors for puerperal endometritis among twins, but a distinction between elective and emergent cesareans was not clearly defined. The increased puerperal infectious morbidity shown by this Finnish group was supported by Alexander et al. [1] who found a relatively high rate of metritis (18%) among their cesarean sections performed in twins. Importantly, the hypothesis proposed by Suonio and Huttunen [10], suggesting that the larger placental bed in twins might be more susceptible to endometritis and thus leading to puerperal infectious morbidity could not be confirmed by our much larger data set.

We conclude that, at present, no solid data exist to show a disadvantage of a planned cesarean birth for twins. Having said this may not suggest that all twins should be delivered by cesarean section, but just to question the concerns that were raised regarding elective cesareans in twins. However, the trend of increased febrile puerperal morbidity following cesarean birth in twins requires further confirmation.

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Chapter V. Discussion

V.Discussion

Portugal, just like most countries in the world, experienced a rise in twin pregnancy rates throughout the past few decades. Using the figures presented by the Portuguese *Instituto Nacional de Estatistica* (INE), we can observe a slow but continued increased in twin pregnancy rates from 1.5% in 1980 to 3% in 2009, figure 34.

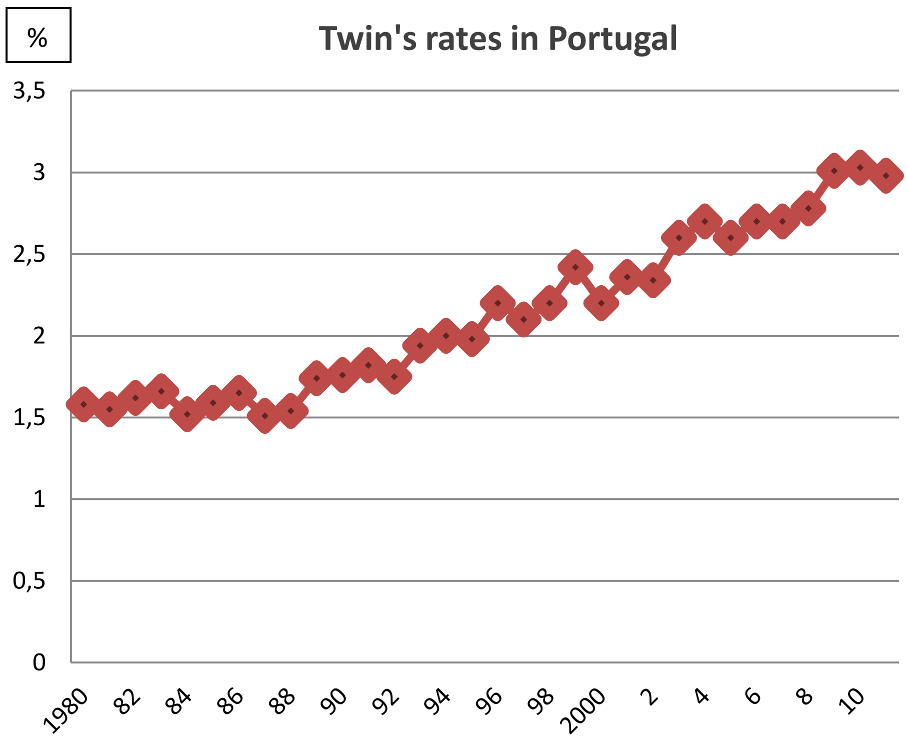

Figure 34 - Twins prevalence in Portugal 1980-2011 (INE information)

Because twins are, in our days, not simply a spontaneous rarity but very often the reward of a long journey through infertility treatments, the survival of two healthy babies becomes the only acceptable outcome of these high risk pregnancies.

An early and effective diagnostic of fetal or maternal problems and the ability to choose the optimal timing and mode of delivery of twins constitute the best tools in avoiding an unpleasant outcome.

1. Abdominal circumference ratio for the diagnosis of intertwin birth weight discordance.

Divergent growth in a twin pair, especially if they are MC twins, is a signal that both twins could be in danger: the small twin in danger of demise and the survivor twin in danger of neurological impairment. We evaluated the risks to the survivor twin [155] in 9 cases of single intrauterine demise of one fetus. Between 1994 and 1998, 235 twin pregnancies were followed in the Multiple Pregnancy Outpatient Clinics at Maternidade Dr. Alfredo da Costa (MAC). Single fetal death above 13 weeks of gestation occurred in 9 cases (3.8%). The cause of fetal death was established in five cases, four of which were due to TTTS. The rate of premature delivery of the surviving twins was 44.4% (4/9) and the rate of mortality was 11.1% (1/9). Neonatal morbidity rate was 62.5% (5/9), mainly related to prematurity. Neurological morbidity rate was 37.5% (3/8) and major neurological lesions occurred in 25% (2/8) of term newborn infants. TTTS was associated with the worst prognosis concerning the surviving twin, Table 14.

Table 14 - Outcomes of the survivor twins.

Adapted from: Martins et al. [155]. *Morte Fetal de um gémeo – Que problemas para o gémeo sobrevivente?* Acta Pediat Port. 2000; 4:303-310

Cases	Gestational age at demise	Cause of fetal death	Gestational age at delivery	Mode of delivery	Sex	Apgar score	Birth weight (g)	Neurological evaluation
1	15	Unknown	38	Vaginal	M	9/10	2800	Normal
2	15	Unknown	40	CS	M	8/10	2290	Normal
3	17	Unknown	38	Vaginal	F	9/10	2450	Normal
4	21	TTTS	38	CS	F	9/10	2300	Cerebral palsy
5	25	TTTS	26	Vaginal	M	1/6	857	Normal
6*	26	Unknown	36	CS	M	9/10	2460	Normal
7	29	Malformation	30	CS	M	9/10	890	Mild neurodevelopment impairment
8	31	TTTS	38	CS	F	9/10	3200	Cerebral palsy
9	34	TTTS	34	CS	F	2/7	2250	Normal

*DC twin. All the others were MC twins

All our cases with neurological morbidity associated with fetal demise were MC twins.

Discordance of at least 20% led to complications in about 16% of twin gestations [28]. Adegbite et al. [78] found a higher incidence of neurological morbidity in both MC and DC twins with discordant birth weight, when compared with a concordant group.

Several authors have reported fewer implications of intertwin discordance if the small twin is not small for its gestational age [156,157]. Selective intrauterine growth restriction occurs in about 12% of twin pregnancies [160]. The incidence of this process is similar in DC and MC twin pregnancies, but the risk of neurological damage is greater in MC twins [161,162].

Gratacós et al. [163] confirm that pregnancies involving IUGR are associated with a high risk of intrauterine demise of the growth restricted fetus but also provided considerable evidence that even in the cases where the growth-restricted twin survived, there was a high risk of perinatal leucomalacia, especially if intermittent /absent or reverse end-diastolic umbilical artery flow velocity were observed.

Ever since the clinical implications of inter-twin discordant growth have been clarified, several sonographic measurements have been used in an attempt to diagnose this complication.

In our first study - **Abdominal circumference ratio for the diagnosis of intertwin birth weight discordance**, we assessed the accuracy of the abdominal circumference (AC) and the estimated fetal weights (EFW) difference in predicting discordant twin growth. We found that the accuracy of an EFW in predicting actual birth weight was rather poor, and that a ratio of 1.3 between paired AC was the most adequate method, predicting severe birth weight discordance with a very high sensitivity (97.3-100%) and specificity (99.6-99.7) values.

One of the main advantages of this is that AC measurement is easy to perform and does not require a very skilled sonographer. In high risk situations, it can therefore be repeated as often as necessary as part of routine evaluations. Additional, more thorough sonographic measurements by an expert can then be requested when discordant growth is detected.

2. Perinatal Outcome and Change in Body Mass Index in Mothers of Dichorionic Twins: A Longitudinal Cohort Study

Several interventions have been attempted in order to optimize the results of twin pregnancies, such as specialized programs with hyper caloric dietary and multimineral supplementation, prescribed to reduce the rates of very preterm and very low birth weight infants [158]. The University of Michigan Multiples Clinic had a prenatal regimen that included twice-monthly prenatal visits to a registered dietitian and nurse practitioner team in addition to regular prenatal visits with the woman's primary care physician, additional maternal education, modification of maternal activity, individualized dietary prescription, multimineral supplementation, and serial monitoring of nutritional status.

Each program participant received a dietary assessment on entry to the program, based on a 24-hour dietary recall, and, if needed, recommendations were made to bring the diet to 3000 to 4000 kcal/day, depending on pregravid body mass index (BMI).

When they evaluated the effectiveness of this specialized program [158] they found an improvement in pregnancy outcomes: preeclampsia [Adjusted OR 0.41 CI (0.23-0.75)]; PPROM [Adjusted OR 0.35 CI (0.20-0.60)]; delivery <36 wks [Adjusted OR 0.62,CI(0.43-0.89)]; LBW [Adjusted OR 0.42 CI(0.29-0.61)]; significant longer gestations (+7.6 days); higher birth weights (+220g); lower neonatal morbidity [Adjusted OR 0.44 CI(0.31-0.62)], lower length of stay (-5.3 days), and lower cost per twin (-$14,023), Figure 35.

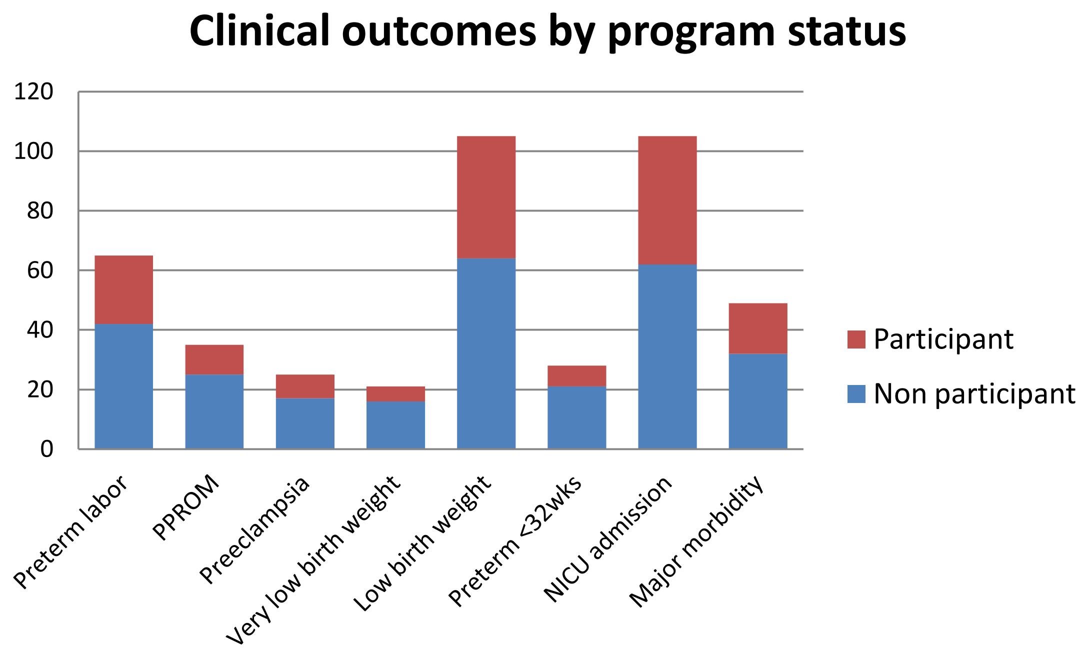

Figure 35 - University of Michigan Nutrition Intervention Program rates of twin pregnancy outcomes (all differences p<0.01).

Adapted from: Luke et al. [158] *Specialized prenatal care and maternal and infant outcomes in twin pregnancy.* Am J Obstet Gynecol 2003; 189:934-938.

In our second paper - **Perinatal Outcome and Change in Body Mass Index in Mothers of Dichorionic Twins: A Longitudinal Cohort Study,** we did not find an association between maternal weight gain, in terms of change in BMI, and outcomes, in term of gestational age at birth and total twin birth weight. We believe that the most important factor potentiating the improvements in clinical outcomes for the program at Michigan University was not the hyper caloric dietary, but rather the prenatal care and patients' education on environmental and work hazards, physical activity and signs of preterm labor. Of additional importance were the recommendations for work leave after 24 weeks of gestation (or sooner in the case of stressful physical or mental work, or antenatal complications) as well as the recommended decrease in stair climbing, strenuous lifting or carrying, and the limiting of recreational activities such as walking or swimming, as it is known that this kind of activities increases the risk of preterm labor.

Vintzileos et all [159] found that a lack of prenatal care among twin gestations was associated with a 1.24-fold increased preterm birth rate among black women and 1.22-fold increased rate among white women, with much stronger associations between lack of prenatal care and births at < 32 completed weeks gestation.

Table 15 - Association between prenatal care and twin preterm birth among white and black women. USA (1889-2000).

Adapted from: Vintzileos et al. [159] *The impact of prenatal care on preterm births among twin gestations in the United States, 1989-2000*. Am J Obstet Gynecol. 2003; 189: 818-823.

	Prenatal care present		**Prenatal care absent**			
Group	**Total twin births**	**Twin preterm birth N (%)**	**Total twin births**	**Twin preterm birth N (%)**	**Adjusted RR (95%CI)**	**Adjusted population attributable risk (%)**
White women						
<32 wks gestation	363,642	54,382(15)	3,403	1,368(40.2)	2.65(2.07-3.28)	19.8
Black women						
<32 wks gestation	79,333	20,843(26.3)	2,907	1,598(55)	2.11(1.73-2.47)	22.6

Relative risks were adjusted for birth cohort (year), maternal age, gravidity, maternal education, marital status, smoking and alcohol use during pregnancy and antenatal high-risk conditions

Vogel et al. [239] analyzing maternal and perinatal outcomes in twin pregnancies from 23 low and middle income countries found an improve in perinatal survival according with the number of antenatal care visits, table 16

Table 16 - Factors associated with adverse perinatal outcomes in twin pregnancies in 23 low- and middle-income countries.

Adapted from Vogel et al [239] *Maternal and Perinatal Outcomes of Twin Pregnancy in 23 Low- and Middle-Income Countries* PLoS ONE 8(8): e70549. doi:10.1371/journal.pone.0070549

Antenatal care visits	Perinatal mortality N=461(%)	Perinatal survival N=6,001(%)	Crude OR(95%CI)
0	52(11.3)	323(5.4)	3.28(2.36-4.55)
1-3	184(39.9)	1,444(24.1)	2.60(2.10-3.21)
4 or more	186(40.3)	3,789(63.1)	Reference
Missing	39(8.5)	445(7.4)	

Visits to our Multiple Pregnancy Outpatient Clinics at MAC involve discussions on diet (but few dietary interventions), work, intercourse, signs and symptoms of premature contractions, urinary complaints, vaginal discharge, anemia, preeclampsia, fetal movements, and alarming sights such as bleeding or PROM. In these patients we noticed a lower rate of spontaneous delivery < 32 weeks, with 78 cases in a cohort of 1588 twins (4.9%).

Our study - **Perinatal Outcome and Change in Body Mass Index in Mothers of Dichorionic Twins: A Longitudinal Cohort Study** debunked the myth of the need for hypercaloric diets, which are associated with a risk of excessive weight gain and future obesity, in order to achieve successful results in multiple gestations.

3. <u>Gestational Diabetes Mellitus Complicating Twin Pregnancies.</u>

Diabetes mellitus is a frequent gestational complication affecting 2-10% of pregnancies [164]. Luo and al. [165] conducting a retrospective cohort-based study of singleton and twin births (n=15,974,433) in the USA found that diabetes complicated 3.5% of twin and 2.7% of singletons pregnancies. In our third paper- **Gestational Diabetes Mellitus Complicating Twin Pregnancies,** we found a higher rate of gestational diabetes (7.8%) but our hospital is a tertiary and perinatal referral center, where problematic twin pregnancies are usually sent to for management.

In a previous evaluation [166] performed in 2009, including only 81 mothers of twins with gestational diabetes we also found a prevalence of diabetes mellitus of 8%. In this first evaluation we used the remaining 902 twins of the database as the control group and found several other conclusions, Table 17.

Table 17 - Gestational diabetes in twin pregnancies.

Adapted from Queirós et al. [166]. Porto 2009 (Poster presentation)

	GDM twins N=81	**No GDM twins N=902**	**p**
Maternal age (Y)	31.4	30.2	0.045
Nulliparity (%)	88.9	86.4	ns
Mean BMI(kg/cm^2)	25.9	23.5	<0.001
BMI≥30 kg/cm^2 (%)	18.5	6.5	<0.001
Mean weight gain per week	0.474	0.491	ns
ART pregnancies (%)	22.2	15.5	0.082
MC twins (%)	10.3	7.3	0.075
DC twins (%)	89.7	92.7	
Deliver<32 w (%)	12.3	6.6	0.053
Hypertensive disorders (%)	28.8	18.6	0.04
Cholestasis (%)	11.1	3.1	0.002
Mean Birth weight(g)	2,188	2,268	ns

Using a logistic regressive model we found that obesity was the major independent risk factor for gestational diabetes in twins. Pregnancies resulting from ART and MC twins also had a higher risk of GDM, Table 18.

Table 18 - Risk factor for GDM in twin pregnancies.

Adapted from Queirós et al. [166]. Porto 2009 (Poster presentation)

	p	Odds ratio	CI 95%
Obesity	<0.001	3.63	1.93-6.82
Monochorionicity	0.050	1.65	1.00-2.71
ART	0.028	1.94	1.07-3.48

It is likely that a larger control group (albeit no longer as good a match in terms of gestational age and year of delivery) could give additional power to the statistical results.

Luo and al. [165] observed a significant protective effect of GDM pregnancies against low 5-min. Apgar score and neonatal death for twins but not for singletons (adjusted odds ratio 0.74). Although in both our studies we did not find significant differences in the GDM group with respect of low Apgar score and neonatal deaths compared with the control group of no GDM twin pregnancies.

Our paper- **Gestational Diabetes Mellitus Complicating Twin Pregnancies** shows that obesity is a risk factor for diabetes and that an increased obstetric surveillance and clinical management of the diabetes by a skilled endocrinologist could allow most of these pregnancies to reach the same gestational age at delivery as the twin pregnancies without GDM. However, it is worth remembering that even at the same gestational age newborns from GDM mothers face more respiratory distress syndrome (OR 2.2; 95% CI 1.3-3.7), which has recently led us to adopt a policy of antenatal steroids, in order to mitigate this problem.

4. Prospective Risk of Intrauterine Death of Monochorionic Diamniotic Twins.

Single IUFD is a relatively rare event in a twin pregnancy that occurs in 2 to 7% of the cases [118]. However, the death of a twin in MC pairs could bring devastating consequences to the survivor; neurodevelopmental impairment could occur in 26% of the cases [118]. Sebire et al. [160] noted a risk of perinatal loss in MC twins only slightly higher than in DC twins (4.9% vs 2.8%). Barigye et al. [154], in a well-structured study, observed a risk of 4.3% of fetal demise in uncomplicated MC pregnancies at 32 weeks of gestation, and concluded that this might be obviated by a policy of elective preterm delivery. The publication of these results, in 2005, triggered a complete change in paradigm regarding the management of MC pregnancies, leading to a rise of elective preterm CS, both to avoid emergent CS and to obviate the risks of acute TTTS during labor [168].

More than simply propose elective preterm deliveries as a solution, Barigye's results suggested CS for all MC twins. Even in our department at MAC, it proved difficult to maintain existing policies, with ultrasonographers advising couples that after 32 weeks they could not ensure the wellbeing of the two MC fetuses, and that elective preterm CS was the least dangerous solution.

Our fourth paper - **Prospective Risk of Intrauterine Death of Monochorionic Diamniotic Twins**, published in 2006, was the first in disagreement with Barigye and worked as a plug to this policy. We showed that even using our entire MC twin cohort, rather than just the uncomplicated ones, and performing vaginal deliveries, our prospective risk after 32 weeks was much lower (1.2% per pregnancy) than the one reported by Barigye.

Cleary-Goldman et al. [179] in 2005 suggested delivering MC-DA twins at 34-35 weeks of gestation, following antenatal steroids administration and reported no unexplained IUFD. Just like our group, they conducted antenatal surveillance more frequently than once every two weeks and used non-stress tests in addition to ultrasound and Doppler studies.

Several other papers on this topic were published in the next few years. In 2007, Acosta-Rojas et al. [169] analyzing a cohort of 127 MC twins, observed an incidence of intrauterine fetal death of 6.5%. However, TTTS was responsible for 5 deaths in ten cases with this complication and IUGR accounted for 2 deaths in 9 cases where this condition was present.

In 2008, Hack et al. [182], analyzing 1,053 of 1,305 pregnancies delivered after 32 weeks of gestation in a tertiary referral center and a general teaching hospital, both in The Netherlands, found that the IUFD rate in continuing pregnancies after 32 weeks of gestation was 2.1% in MC twins and 0.3% in DC twins; HR 8.75, 95% CI (2.65–28.88).

Lee et al. [184], analyzing 1,000 consecutive twin gestations (196 MC and 804 DC twins) from a single tertiary care center, found a prospective risk rate of IUFD of 1.7% after 32 weeks in the 130 uncomplicated MC pairs. They usually offered elective delivery at 34-35 weeks for uncomplicated MC-DC twins after corticosteroid administration or confirmation of fetal pulmonary maturity.

In 2008, Lewi et al. [73], analyzing a cohort of 202 twin pairs, also reported 1.2% as the prospective risk of intrauterine fetal death after 32 weeks, and 0.7% at 36 weeks. On the other hand, Ortibus et al. [170], in 2009 and after analyzing 138 MC pregnancies, reported that in 4% of the cases an IUFD occurred and in 6% both twins died in uterus. However, looking carefully at the causes of mortality, 13 in 18 could be related to TTTS and the other ones to discordant growth.

Domingues et al [178] in 2009, analyzing a database of 576 multiple pregnancies managed at Coimbra University Hospitals between 1996 and 2007, selected the uncomplicated ones: 111 MC and 290 DC twins delivered after 24 wks. Unexpected single intrauterine deaths rate was 2.7% in MC versus 2.8% in DC twins. The prospective risk after 32 weeks was 1.3% for MC and 0.8% for DC twins.

In 2010, Smith et al. [171], analyzing the entire cohort of 345 ongoing MC pregnancies at 24 weeks found that the prospective risk of IUFD from 24 weeks onward was 2.3% and 1.6% from 32 weeks. By comparison, at 24 weeks, they had 234 (68%) ongoing pregnancies that were uncomplicated by TTTS or severe discordance, for which the risk of IUFD at 24 and 28 weeks was 1.3% and at 32 weeks was 0.5%. They found a total of 1 single and 2 double IUFDs in the uncomplicated group, the first was a single loss at 33 weeks in a patient with sudden-onset severe preeclampsia, and the second a double IUFD in a pair with 20% of growth discordance. They concluded that the number of uncomplicated pregnancies that would need to be delivered preterm at 32 weeks to prevent 1 IUFD was 201 corresponding to 402 fetuses.

Although infant mortality rates for babies born between 32 and 36 weeks is low [172], Refuerzu et al. [232] reported an eightfold increase in the risk of respiratory morbidity compared with term infants, and Petrini et al. [173] have suggested that children born between 34 and 36 weeks were more than three times as likely as those born at term to be diagnosed with cerebral palsy.

Smith et al. [171] suggested that we should consider prolonging pregnancy to 36 or 37 weeks in the absence of a clinical indication for delivery in MC-DA twins.

Hack et al. [180] in 2011, analyzing a cohort of 465 MC twins reported a prospective risk of single IUFD after 32 weeks in ongoing pregnancies of 0.2% and a risk of double IUFD of 0.4%.

In the same year, Tul et al. [167] used a population-based study of 387 MC-DA twins followed and delivered after 24 weeks in Slovenia during the period 1997–2007 and reported a higher risk. There were 32 fetal deaths in a total of 774 fetuses (4.1%; 95% CI, 3.0%–5.9%) and the prospective risk of stillbirth per pregnancy after 33 weeks of gestation was 6.2% (95% CI, 4.2%–9.1%). In Slovenia, 3.6% of the MC-DA pregnancies ended during the study period without any surviving infant. At the same time none of the neonates born after 34 weeks died, so they concluded that MC twins may benefit from elective preterm birth.

Still in 2011, Glinianaia et al [174], analyzing a population-based study of 4,565 twin pregnancies reported a stillbirth rate of 4.4% and 1.2% respectively in MC and DC twins, with a higher risk before 28 weeks and no apparent rise in later gestations.

In another 2011 paper, Morikawa [114] analyzed a total of 3,241 MC twins and reported a prospective risk of IUFD of 2.5% at 22 weeks of gestation and <1 % at ≥32 weeks.

Sullivan et al. [175], in 2012, made one evaluation of a total of 3,799 twins, 852 MC and 2,947 DC twins, delivered during a period of 9 years at 18 hospitals in the USA. When adjusted for maternal age, race, ethnicity, marriage status, and parity they noted a 3-fold risk of total fetal mortality in MC-DA twins when compared to DC twins The gestational age-specific prospective risk of perinatal mortality was not different between the 2 groups at >28 completed weeks of gestation. At 32 weeks, the risk of perinatal death in MC-DA twins was 0.14% and increased to a maximum of 0.46% at 37 weeks (p=0.13). They also observed that in a cohort of twins who did not have medically indicated deliveries the risk of serious adverse perinatal events at >31 weeks was no different between MC-DA and DC twins. Severe adverse perinatal events were significantly greater in MC-DA fetuses delivered at every gestational week (until 36 completed weeks) when compared to MC-DA fetuses delivered in subsequent weeks. Importantly, they noticed that neonatal care charges were significantly higher in MC-DC twins delivered <36 wks.

In 2012, The Southwest Thames Obstetric Research Collaborative (STORK) [176] analyzing 3,005 twin pregnancies found that the risk of stillbirth in MC twins did not change significantly between 26 weeks (0.18%) and 36 weeks (0.34%) with an OR of 1.85, 95% CI (0.3-13.2). They concluded that the data did not support a policy of elective delivery before 36 weeks of gestation in MC twins.

Breathnach et al [177], in 2012, after analyzing a cohort of 1,001 twin pairs, found 1.5% as the prospective risk of stillbirth after 34 weeks for uncomplicated MC-DA twins, and noted that the risk of a composite measure of perinatal morbidity for uncomplicated MC twins fell from 41% at 34 weeks to 5% at 37 weeks (p<0.001). They concluded that with a strategy of close fetal surveillance, perinatal morbidity could allow uncomplicated MC pregnancies to continue to 37 weeks.

In summary (Figure 36), different authors in different countries with different cohorts have found slightly different values of prospective risk of IUFD in MC twins. However there were several kinds of data origins:

1. From single tertiary referral center (as in our study and Domingues)
2. From several tertiary referral centers (as Ortibus and Breathnach)
3. From population-based studies (as Glinianaia and Tul)

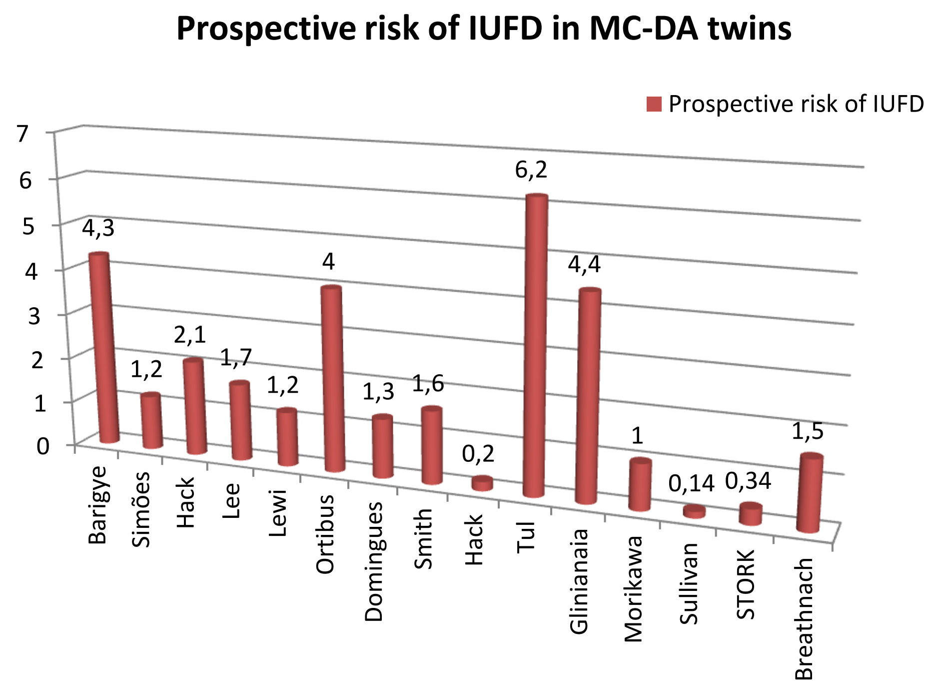

Figure 36 - Prospective risk of single IUFD at 32 wks in MCDA twins according to several studies.

Population-based and multicenter studies observed a higher rate of IUFD compared with single tertiary referral centers, such as our center. A more tailored surveillance including weekly assessment and the use of other tests such as non-stress tests in addition to ultrasound and Doppler studies could be responsible for the lower rate of IUFD in our population, as in other referral centers.

In another evaluation recently performed by our group, analyzing the full cohort of 438 MC-DA twins delivered after 24 weeks of gestation, we found an even lower rate of 0.8% for the prospective risk of IUFD after 32 weeks per pregnancy and a prospective risk per fetus of 0.5%.

Table 19 - Fetal demise in MC-DA twins by two weeks interval. (MAC)

	Number of continuing		**Deaths (N) per period per**	
Gestat. age	**Pregnancies**	**Fetuses**	**Pregnancies**	**Fetuses**
24-25 wks	438	876	5	7
26-27wks	433	859	2	3
28-29 wks	425	840	1	1
30-31 wks	406	801	1	1
32-33 wks	378	744	0	0
34-35 wks	316	620	3	4
≥36 wks	215	414	0	0

Looking at the figures, table 19, we would have to perform iatrogenic preterm delivery of 744 fetuses at 32 weeks of gestation in order to avoid four stillbirths.

Finally in 2012, Robinson et al [183] attempted to find the ideal gestational age to deliver uncomplicated MC-DA twins. They compared 9 different strategies (Table 20) for the timing of delivery in pairs with concordant grown and no other complications such as preeclampsia, fetal growth restriction or TTTS. All patients had reached 32 weeks with both twins alive.

They used the quality-adjusted life years (QALYs) for each strategy based on the anticipated life expectancy. Adverse perinatal outcomes that were considered in the model were perinatal death, RDS, cerebral palsy, mental retardation and infant death.

Table 20 - Delivery strategies.

Adapted from: Robinson et al. [183] *Effectiveness of timing strategies for delivery of monochorionic diamniotic twins.* Am J Obstet Gynecol 2012; 207:53.e1-7.

Strategy	Gestational age at scheduled delivery
1	32 wks after steroid administration
2	33 wks after steroid administration
3	34 wks after steroid administration
4	35 wks after steroid administration
5	36 wks
6	36 wks pending amniocentesis
7	37 wks
8	37 wks pending amniocentesis
9	38 wks

Figure 37 presents the ranked QALY outcomes for the different strategies. The differences among the 36, 37 and 38 week strategies were very small and markedly drop-off for the remaining strategies. Amniocentesis did not help to improve the outcome results. They concluded that for otherwise uncomplicated MC-DA twins a scheduled delivery ≥ 36 weeks gestation effectively balances the risks of prematurity with those of stillbirth.

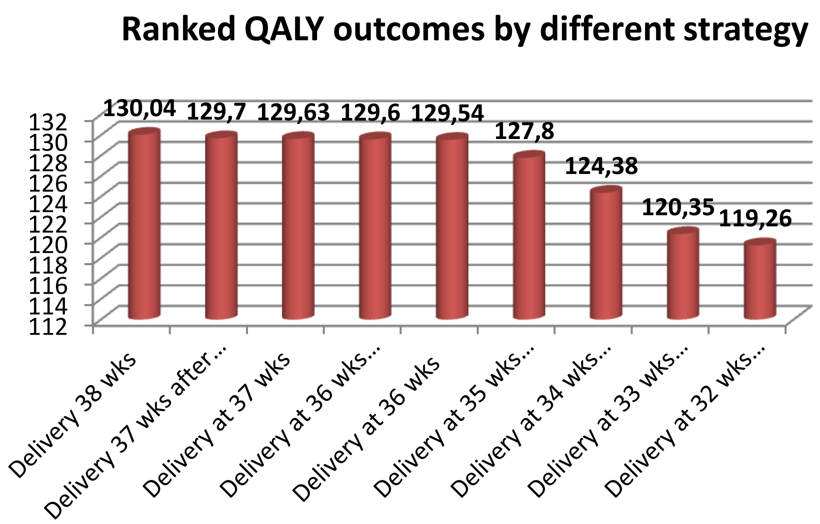

Figure 37 - Ranked QALY outcomes by different strategy.

Adapted from: Robinson et al. [183] *Effectiveness of timing strategies for delivery of monochorionic diamniotic twins.* Am J Obstet Gynecol 2012; 207:53.e1-7.

Our forth paper – **Prospective Risk of Intrauterine Death of Monochorionic Diamniotic Twins**, defending the delivery at 36 – 37 wks keeps up, even our days in accordance to the worldwide guidelines, Table 21.

Table 21 - Worldwide guidelines for the delivery of MCDA twins.

Adapted from: Sela et al [181]. *Timing of planned delivery in uncomplicated monochorionic diamniotic twin pregnancies: a review of the literature*. Expert Review of Obstet Gynecol. 2012; 7:483-491.

Authority	Nation	Year published	Recommendation
Society of Obstetricians and Gynaecologists of Canada	Canada	2000	No recommendation
American College of Obstetricians and Gynecologists	USA	2004	No recommendation
Royal College of of Obstetricians and Gynaecologists	UK	2008	36-37 wks
Royal Australian and New Zealand College of Obstetricians and Gynaecologists	New Zealand and Australia	2011	37 wks
National Institute for Health and Clinical Excellence	UK	2011	36 + 0
Collège National des Gynécologues et Obstétriciens Français	France	2011	>36 to 38+6 wks

5. Induction of Labor with Misoprostol in Nulliparous Mothers of Twins.

Our fifth paper-**Induction of Labor with Misoprostol in Nulliparous Mothers of Twins**, revealed our experience in labor induction in twins. We began performing labor induction in our twins out of a necessity; with the reduction on the rates of spontaneous preterm delivery resulting from a better surveillance in our Multiple

Pregnancies Outpatient Clinic at Maternidade Dr. Alfredo da Costa, we faced a rise in the number of twin pregnancies reaching 38 weeks without spontaneous labor.

Such a high number of twins impeded the scheduling of all our patients for an elective CS, and also gave rise to difficulties in performing appropriate sonographic and Doppler evaluations for all our twins on a weekly basis.

Often, twin gestations were complicated by hypertensive disorders, diabetes, cholestasis or fetal growth restriction and we were afraid to keep them waiting for spontaneous labor due to the risk of IUFD associated with an advanced gestational age, fetal or maternal problems. We therefore made use of the wide experience in labor induction in singletons available in the department, extrapolating our techniques to twins.

We began inducing labor in twin gestations in 1994, initially just on post-term twin pregnancies (>37 weeks) and subsequently on twin pregnancies with less than 37 weeks because of fetal or maternal complications.

The method of labor induction was chosen according to Bishop's score. Those with a score below 5 were given 100µg oral misoprostol (Cytotec ™, Portugal) every 6 hours until Bishop's score was greater than 5. For those with a score above 5 we used oxytocin drips, 10 IU in 1000 ml of glucose-free fluid (10 mIU/ml) in a progressive scheme starting with 10 ml/hour, up to a maximum of 90 ml/hour or regular contractions. We performed amniotomy at 3 cm dilatation. Fetal well-being was evaluated following induction and intrapartum via electronic fetal heart rate monitoring. Internal electronic monitoring of the first twin was performed after amniotomy.

The first evaluation of our results was published in 1999 [185]. This study included 50 consecutive twin pregnancies that underwent labor induction between 1994 and September 1998. This study group was compared with a control group of 93 singleton pregnancies randomly chosen from the labor induction cases during the same period. The indications for labor induction were similar in both groups: maternal or fetal complications that require pregnancy termination and post-term gestations (>38 weeks for twins, >41 weeks for singletons). Selection criteria for labor induction in singletons included vertex presentation with an estimated fetal weight of less than

4.000 g. We excluded all patients with a previous uterine scar. All patients gave their informed consent.

The following variables were compared: maternal age and parity, gestational age at delivery, pregnancy complications, mode of induction and delivery, duration of active phase of labor (from 3 cm to full cervical dilatation), inter-twin delivery interval, birth weights and 5 minute Apgar scores. We used the chi-squared and Mann-Whitney U tests for statistical analysis. A p-value of less than 0.05 was considered significant.

We did not find statistically significant differences between the two groups with respect to maternal age and nulliparity. Preterm labor was significantly increased ($p<0.05$) in the twin group (43% vs. 3%). Other maternal complications were not significantly different (hypertensive disorders 28% vs. 17%; gestational diabetes 12% vs. 8%). The mean gestational age at induction of labor was 37±3 weeks for the study group and 40±3 weeks for the control group. Presentation combinations for the twin group included 68% vertex-vertex, 28% vertex-breech, and 4% vertex-transverse. The duration of the active phase of labor in the study group was studied in 40 patients only (5 patients required cesarean delivery and the data was unavailable for the other 5). Similarly, the duration of the active phase of labor in the control group was studied in 69 patients only (18 patients required cesarean delivery and for the other 6 the data was unavailable). The mean duration was 4:28 hours and 5:25 hours in the study and control groups respectively ($p<0.05$). In 95% of the study subjects vaginal birth was achieved in less than 10 hours, as compared to 91% in the controls ($p<0.05$). The active phase to delivery interval was less than 3 hours in 50% of the study group as compared to 27% in the controls ($p<0.05$). Precipitate labor (active phase to delivery interval less than 1 hour) was almost the same in both groups (5% vs. 5.8%). The mean inter-twin delivery interval was 13 min (range 2-34 min).

The mode of delivery in both groups was not significantly different. In the study group there were 88% vaginal births vs. 80.6% in the controls. Combined (vaginal/CS) twin delivery was done in 2% of the study twins. The two groups had similar perinatal morbidity. We recorded one 5 minute Apgar score <7 because of a prolapse of the cord in the second twin. As expected, the mean birth weight of twins was lower than that of singletons (2587 g vs. 3273 g). In the study group there were no babies weighting less than 2000 g and 60% of the twins weighted more than 2500 g. All babies of the control group weighted more than 2500g.

This study has provided reassuring evidence about the safety of labor induction in twins. In addition, it indicated that the active phase was shorter in twins following induction than in singletons.

We have recently conducted another evaluation, selecting all 1040 twins delivered at 35 or more weeks with both twins alive. 779 were DC and 261 MC-DA. 196 DC and 77 MC-DA twins underwent labor induction, Figure 38.

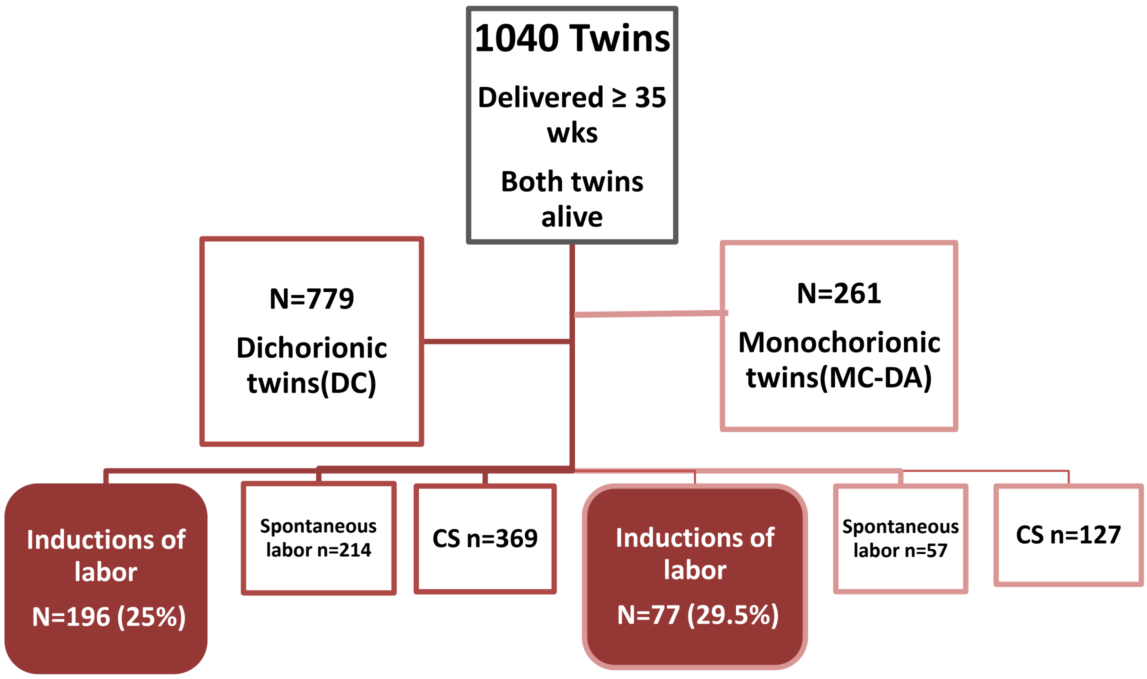

Figure 38 - Database from the Twins Outpatient Consultation at MAC (2012)

We compared labor inductions in DC and MC twins, and found that in 25.5% and 29.9%, respectively, the second twin was not in a vertex presentation. Spontaneous pregnancies were more frequent in the MC-DA twins and hypertensive disorders in the DC group. We did not find statistically significant differences between both groups with respect to nulliparity rate, BMI, history of premature contractions, diabetes and discrepancy ≥25%, Table 22.

Table 22 - Labor induction in DC and MC-DA twins –

Adapted from: Simões [186]: *Should we induce twins?* The 17th World Congress on Controversies in Obstetrics, Gynecology & InfertilityLisbon, Portugal, November 8-11, 2012

	DC twins n=196	**MC-DA twins n=77**	**p-value OR(95%CI)**
Age (years)	30±4.6	30±5.6	P=0.99
Nulliparous	116(59.2%)	48(62.3%)	P=0.6 OR: 0.5 95%CI (0.49-1.48)
Spontaneous pregnancy	143(73%)	71(92.2%)	**P=0.0002** **OR: 0.23** **95%CI (0.085-0.53)**
BMI(kg/m^2)	23.8±4.3	22.9±4.4	P=0.127
Premature contractions	79 (40.3%)	35 (45.5%)	P=0.44 OR: 0.81 95%CI (0.47-1.38)
Hypertensive disorders	38 (19.4%)	7 (9.1%)	**P=0.035** **OR:2.4** **95%CI (1.05-6,07)**
Diabetes	19(9.7%)	9(11%)	P=0.6 OR:0.81 95%CI (0.35-1.96)
Discrepancy ≥25%	9(4.6%)	3(3.9%)	P=0.84 OR:1.186 95%CI (0.32-5.56)

MC twins had a lower mean gestational age at delivery, a higher rate of CS, a lower mean duration of the active phase of labor and a lower mean inter-twin interval, Table 23. Those results could mean that when labor is taking too long in MC twins a more interventionist approach is adopted by the obstetric team.

In fourteen cases (7.1%) of the DC twins and four cases (5.2%) of the MC twins we needed a combined delivery (vaginal for the first twin and CS delivery for the second one), Table 23. This value is lower than the one reported by Alexander et al. [242] with 17% of combined delivery, but closer to the 4.3% reported by Persad et al. [243]. The primary adverse outcomes of a combined delivery are an increased risk of puerperal infection, an increased postoperative recuperation time and the impact on future pregnancies resulting from cesarean delivery [244].

Table 23 - Labor induction in DC and MC-DA twins, gestational age at delivery and mode of delivery

Adapted from Simões [186]: *Should we induce twins?* The 17th World Congress on Controversies in Obstetrics, Gynecology & Infertility, Lisbon, Portugal, November 8-11, 2012.

	DC twins n=196	**MC-DA twins n=77**	**p-value OR(95%CI)**
Gestational age at delivery (wks)	36.8±0.9	36.4±0.8	P=0.002
Deliveries ≥ 36 wks	178 (90.8%)	71 (92.2%)	P=0.74 OR:0.83,95%CI (0.29-2.14)
Vaginal-Vaginal	167 (85.2%)	59 (76.6%)	P=0.1
Vaginal-CS	14 (7.1%)	4 (5.2%)	P=0.59 OR:1.4,95%CI (0.46-5.09)
CS	15 (7.7%)	14 (18.2%)	P=0.01 OR:0.37,95%CI(0.169-0.83)
Mean duration of the active phase of labor (min)	260 ±2.8	210 ±94	P=0.01
Mean inter-twin interval (min)	12.1±9.8	9.1±8	P=0.03

MC-DA twins had a lower mean birth weight of the 1st twin and a lower mean length of stay of the 2nd twin. We did not find statistically significant differences with respect to mean length of stay of the 1st twin, Apgar score<7 at 5', fetal mortality and asphyxia (Table 24), which reassures us about the safety of labor induction in MC-DA twins.

Table 24 - Labor induction in DC and MC-DA twins.

Adapted from Simões [186]: *Should we induce twins?* The 17th World Congress on Controversies in Obstetrics, Gynecology & Infertility, Lisbon, Portugal, November 8-11, 2012.

	DC twins N=196	**MC twins N=77**	**p-value OR(95%CI)**
Mean Birth weight 1st twin (g)	2,519±325	2,430±282	P=0.035
Mean Birth weight 2nd twin (g)	2,454±341	2,377±322	P=0.08
Apgar score<7 at 5'	2 cases 1st twin 2 cases 2nd twin	0 1(2nd twin)	P=0.75
Fetal mortality	1 (trissomic 18 fetus)	1 (Major cardiac malformation)	P=0.56 OR:0.39,95%CI (0.01-15.4)
Mild fetal asphyxia	5(1.3%)	0	P=0.18
Mean length of stay 1st twin (days)	2.9±1.8	2.6±1.2	P=0.1
Mean length of stay 2nd twin (days)	3±2.2	2.5±0.9	P=0.008

Labor induction in twins proved to be safer to the mothers, with few side effects and with no cases of uterine rupture, Tables 25.

Table 25 - Labor induction in DC and MC-DA twins.

Adapted from: Simões [186]: *Should we induce twins?* The 17th World Congress on Controversies in Obstetrics, Gynecology & Infertility, Lisbon, Portugal, November 8-11, 2012.

Maternal morbidity	DC twins N=196	MC twins N=77	p-value OR(95%CI)
Post partum hemorrhage(n)	10(5.1%)	2(2.6%)	P=0.39 OR:2.01,95%CI (0.48-13.8)
Fever(n)	4	0	-
Uterine rupture(n)	0	0	-
Mean maternal length of stay in the hospital (days)	2.65±1.04	2.53±0.73	P=0.35

Including both DC and MC-DC twins, we found a total of 244 (89.4%) vaginal deliveries with labor induction, Figure 39, which is naturally higher than the one achieved in our fifth paper- **Induction of Labor with Misoprostol in Nulliparous Mothers of Twins**, in which we had only analyzed nulliparous mothers of twins, but very similar to the 88% found in our first evaluation published in 1999 [185].

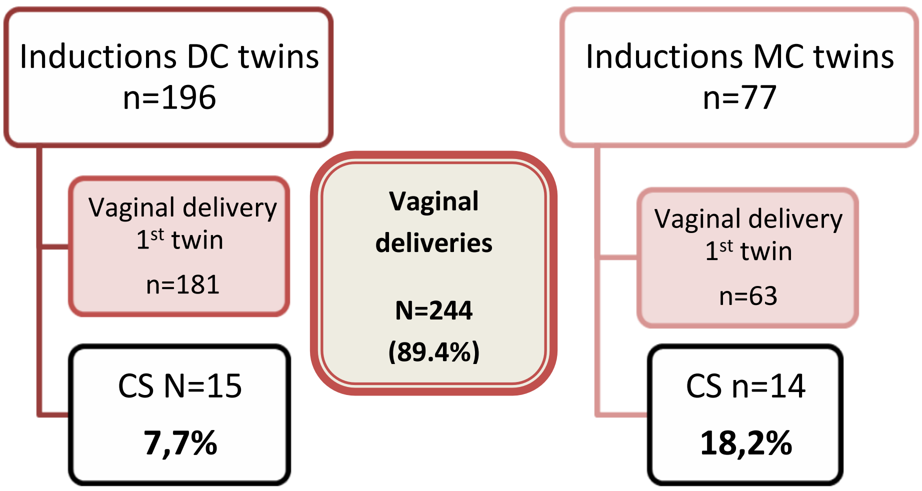

Figure 39 - Mode of delivery in induced twins.

Adapted from Simões [186]: *Should we induce twins?* The 17th World Congress on Controversies in Obstetrics, Gynecology & Infertility, Lisbon, Portugal, November 8-11, 2012.

As in singletons, higher parity and a good pre-labor condition of the cervix are believed to be important predictors of successful induction in twins. However, Park et al. [187] found a significantly lower mean BMI in women who had successful induced labor and, using a multiple logistic regression, demonstrated that only BMI provided a significant contribution in predicting a successful labor induction.

Excessive weight gain during pregnancy, labor induction and high birth-weight of the first-born twin were, according to the literature [188], independently associated with an increased risk of cesarean delivery in labor in twins. Analyzing our database, we compared the successful vaginal delivery group (n=244) with the unsuccessful group (n=29), Table 26.

Table 26 - Risk factors for unsuccessful vaginal delivery.

Adapted from: Simões [186]: *Should we induce twins?* The 17th World Congress on Controversies in Obstetrics, Gynecology & Infertility, Lisbon, Portugal, November 8-11, 2012.

	Successful vaginal delivery n=244	**Unsuccessful n=29**	**p-value OR(95%CI)**
Nulliparous	140 (57.4%)	24(82.8%)	**P=0.007 OR: 3.6 (1.37-10.78)**
Vertex-Vertex presentation	175(71.7%)	22(75.9%)	P=0.7 OR:1.24 (0.51-3.24)
Premature contractions	104(42.6%)	10(34.5%)	P=0.4 OR:0.7(0.30-1.58)
Mean final maternal weight(kg)	80.2±13	77.6±12	P=0.59
Pre-pregnancy Mean BMI (kg/m^2)	23.5±4.3	23.6±3.9	P=0.34
BMI >29(kg/m^2)	26(10.7%)	3(10.3%)	P=0.9 OR:1.03(0.32-4.56)
Mean birth weight 1st twin (g)	2,498±320	2,453±274	P=0.47

We only found statistically significant differences with respect to a prior vaginal delivery, with nulliparity representing a negative predictive factor for a successful labor induction, Table 26.

Induction of labor is significantly associated with CS in singleton pregnancies [189,190]. As such, we selected from our database the twin pairs with spontaneous labor, whom at the same time met the criteria for vaginal delivery: first twin in a vertex presentation and women with no previous uterine surgery, n=192. We then compared DC with MC-DA twins, Figure 40.

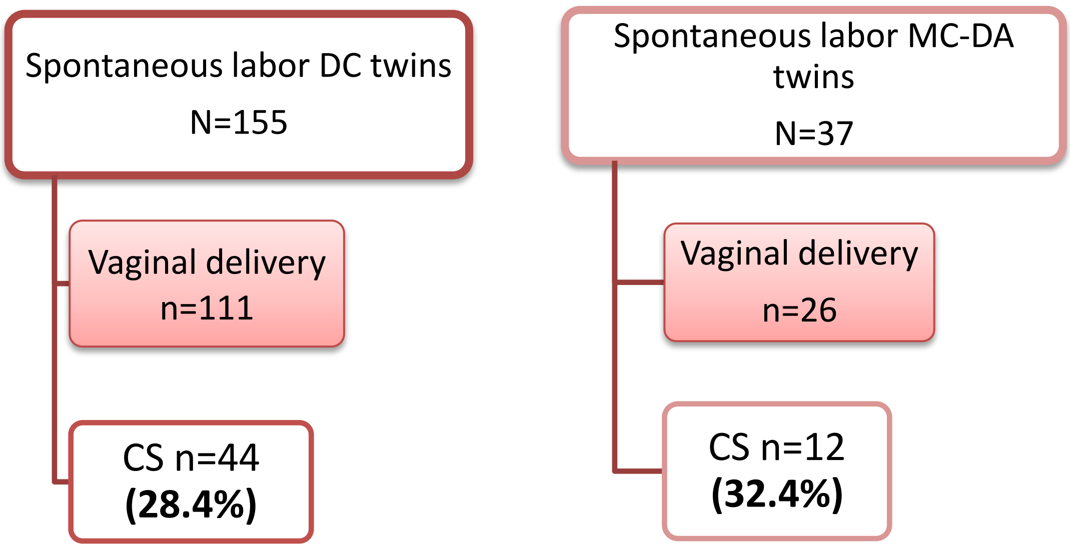

Figure 40 - CS rate in spontaneous labor DC and MCDA twins

Adapted from: Simões [186]: *Should we induce twins?* The 17th World Congress on Controversies in Obstetrics, Gynecology & Infertility, Lisbon, Portugal, November 8-11, 2012.

We found a statistically significant difference in DC twins between the labor induced group and the spontaneous labor group with respect to CS rate, with the first group presenting a much lower rate, $p<0.001$, OR: 4.76 (95% CI:2.56-9.19), figure 41.

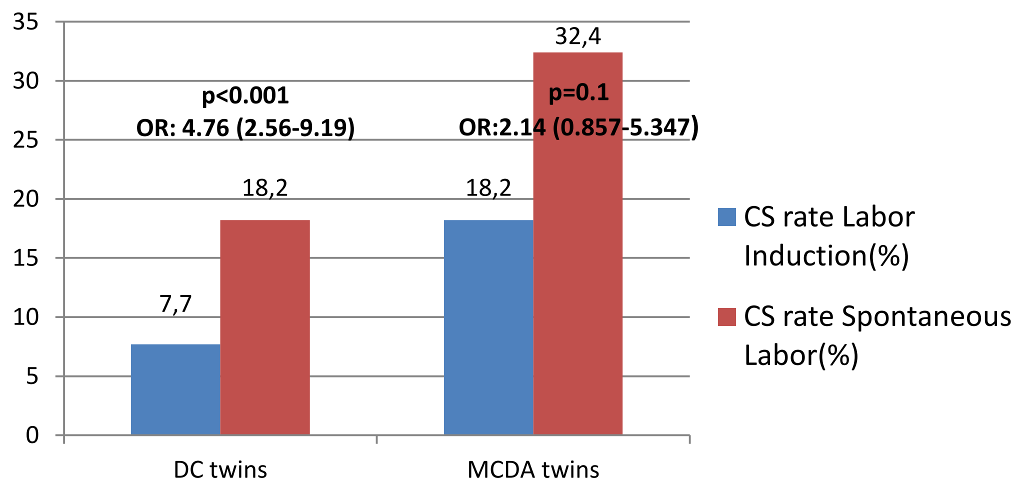

Figure 41 - CS rate in labor induced and spontaneous labor DC and MCDA twins

Adapted from: Simões [186]: *Should we induce twins?* The 17th World Congress on Controversies in Obstetrics, Gynecology & Infertility, Lisbon, Portugal, November 8-11, 2012.

Before inducing twins we should consider the patient's desires or fears. Waiting mothers of twins are usually extremely anxious towards the end of their pregnancy and labor induction with their known medical staff in a scheduled day can provide much emotional relief. On the other hand, an obstetrical team which is skilled in vacuum, forceps, external version, breech delivery or breech extraction can more easily deliver the second twin and avoid the temptation of to perform a CS during labor for the second twin.

The fear of induction of labor-induced fetal distress should not negate its use. Our fifth paper, reporting our experience in nulliparous mothers of twins (usually associated with the worst results) induced with misoprostol in the same doses used in singletons provided reassuring evidence regarding the safety of this procedure.

6. Puerperal Complications Following Elective Cesarean Sections for Twin Pregnancies.

Our sixth paper – **Puerperal Complications Following Elective Cesarean Sections for Twin Pregnancies** – analyzed the morbidity of CS in twin pregnancies. The incidence of CS in multiples has been rising: in The Netherlands, CS rate increased from

26.0% in 1993 to 36.9% in 2007 [192,135]; In the USA [189] an average annual increase of 5% was observed in the period between 1995 and 2008. In Sweden, between 1973 and 1983, CS delivery for twins increased from 7.7% to 68.9% [245].

Because of fetal mal-presentation of the first twin, or due to a previous uterine scar, up to 60% of all twin pregnancies are normally delivered by CS. Over the past few years, a number of reports have appeared in literature defending CS for all twins [128]. Furthermore, as the experience in obstetric maneuvers declines, the rate of CS tends to grow in twin pregnancies. As such, it is crucial to evaluate complications arising from this increasingly common procedure.

In 2013, analyzing our database, we performed two evaluations. In the first one, we attempted to find the risk factors for cesarean delivery during labor in twin pregnancies.

From our database of 1837 multiple pregnancies we selected the twin gestations with obstetrical conditions for vaginal delivery (n=469) and excluded combined deliveries, Figure 42.

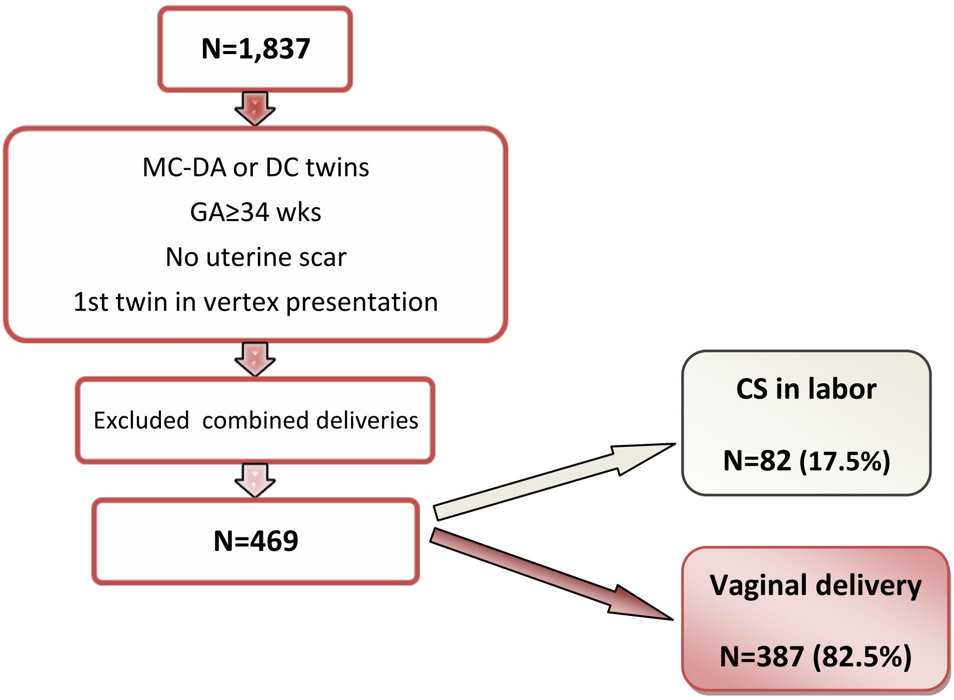

Figure 42 - Population identification (study group).

Adapted from: Correia et al. [193] Risk factors for Cesarean delivery in twin pregnancies .Cesarean Delivery Meeting. Lisbon 19-20 April 2013 (Poster presentation)

The definition of ‘CS in labor’ was used for CS performed during the active phase of labor. Obstetric conditions for vaginal delivery were defined as: MC-DA or DC twins, women with no previous uterine surgery and the first twin in a vertex presentation. In order to avoid confounding biases, we selected only pregnancies ≥34 weeks of gestation.

In 387 (82.5%) of the cases both twins had a vaginal delivery and in 82 (17.5%) cases there was a CS in labor. By comparing these two groups we attempted to identify the risk factors for CS. Analyzing the maternal characteristics, we found statistically significant differences with respect of nulliparity, mean BMI and BMI≥30 (kg/m^2) and labor induction, Table 27.

Table 27 - Maternal characteristics.

Adapted from: Correia et al. [193] Risk factors for Cesarean delivery in twin pregnancies. Cesarean Delivery Meeting. Lisbon 19-20 April 2013 (Poster presentation)

	CS in labor	**Vaginal delivery**	**p-value OR(95%CI)**
Mean maternal age (years)	30±5.4	30±4.5	1
Nulliparity (n/%)	59(72%)	218(56%)	**0.017 OR:1.98 (1.18-3.35)**
Mean BMI(kg/m^2)	22.9±3.2	23.1±4.4	**0.033**
BMI≥30(kg/m^2)	0	25(6.5%)	**0.014 OR:0.09 (0.005-1.43)**
ART pregnancies	17(20.7%)	79(20.4%)	1
Mean gestational age(wks)	36±2.1	36±1.9	1
Labor induction	29(10.8%)	239(89.2%)	**<0.001 0.015(0.009-0.026)**

This evaluation, as observed in the previous ones, confirmed that labor-induced twins have a much lower rate of CS in labor. Conversely, a non-vertex second twin and a birth weight above 2500g were risk factors for CS in labor, Table 28.

Table 28 - Fetal characteristics.

Adapted from Correia et al. [193] Risk factors for Cesarean delivery in twin pregnancies Cesarean Delivery Meeting. Lisbon 19-20 April 2013 (Poster presentation)

	CS in labor	**Vaginal delivery**	**p-value OR(95%CI)**
Chorionicity (MC)	27(32.9%)	103(26.6%)	0.306
Fetal presentation			
Vertex-vertex	39(47.6%)	298(77%)	**<0.001**
Vertex-non vertex	43(52.4%)	89(23%)	**3.69 (2.25-6.05)**
Mean birth weight(g)			
First twin	2,469±347	2,445±334	0.568
Second twin	2,466±384	2,380±320	**0.034**
Second twin>2500g	40(49%)	136(35%)	**0.030** **1.76 (1.09-2.84)**
Apgar score<7 at 5'			
First twin	0	3(0.8%)	1
Second twin	0	4(1%)	1

In conclusion: Nuliparity, [OR: 1.98 (1.18-3.35)], a second twin in a non-vertex presentation**,[**OR: 3.69 (2.25-6.05)]or with a birth weight > 2500g [OR: 1.76 (1.09-2.84)] were identified as risk factors for CS in labor for twins.

In a second evaluation we compared the elective CS with the CS in labor (n=667 vs. 265) and looked for maternal morbidity.

Firstly, it is important to note that the maternal characteristics reported in our sixth paper – **Puerperal Complications Following Elective Cesarean Sections for Twin Pregnancies** – have remained mostly stable throughout the years. However, both nulliparity and mean maternal age have increased, which is in agreement with the steady increase in maternal age at first delivery observed all over the world, Table 29.

Table 29 - Maternal characteristics of twin pregnancies delivered by CS.

Adapted from: Valdoleiros et al. [192] Maternal morbidity following CS for twins. Cesarean Delivery Meeting. Lisbon 19-20 April 2013 (Poster presentation)

	Elective CS N=667	**Labor CS N=265**	**p-value OR(95%CI)**
Mean maternal age (years)	31.2±5.1	30.2±5.7	**P=0.005**
Nulliparity	367(55%)	167(63%)	**P<0.001 OR:0.72(0.54-0.96)**
BMI≥25(kg/m^2)	205(30.7%)	82(30.9%)	P=0.95 OR:0.990(0.729-1.35)
ART pregnancies	151(22.6%)	48(18.1%)	P=0.13 OR:1.32(0.925-1.91)

Table 30 - Problems during pregnancy and mean cervical length at 21-24 wks

Adapted from: Valdoleiros et al. [192] Maternal morbidity following CS for twins. Cesarean delivery Meeting. Lisbon 19-20 (Poster presentation)

	Elective CS N=667	**Labor CS N=265**	**p-value OR(95%CI)**
Premature contractions	229(34.3%)	179(68%)	P<0.001 OR:3.98(2.94-5.39)
Hypertensive disorders	157(23.5%)	37(14%)	P<0.001 OR:1.89(1.29-2.83)
Diabetes	75(11.2%)	25(9.4%)	P=0.43 OR:1.22(0.76-1.99)
Mean cervical length at 21-24wks	2.8±4.6	2.6±2.0	P=0.36

Hypertensive disorders were more prevalent in the elective CS group and premature contraction was, as expected, more common in the labor group (Table 30). However, we did not find statistically significant differences with respect to mean cervical length at 21-24 weeks. This confirms that a normal cervical length at this gestational age in twins does not have the same meaning as in singletons, and in no way should be considered a guarantee of a term delivery. More subtle and continued degrees of cervical insufficiency may lead to early labor and delivery in twins [194].

Table 31 - Mean gestational age at delivery and neonatal outcomes

Adapted from: Valdoleiros et al. [192] Maternal morbidity following CS for twins. Cesarean Delivery Meeting. Lisbon 19-20 April (Poster presentation)

	Elective CS	Labor CS	p-value OR(95%CI)
Mean gestational age at delivery(wks)	35.4±2.2	34.3±2.8	**P<0.001**
Delivery<32wks	41(6.1%)	42(15.8%)	**P<0.001 OR:2.87(1.82-4.55)**
Previous CS	72(10.8%)	22(8.3%)	P=0.13 OR:1.34(0.82-2.24)
Fetal mal presentation	231(34.6%)	109(41.3%)	**P=0.03 OR:0.76(0.57-1.02)**
Fetal distress*	176(26.4%)*	56(21.1%)	**P=0.047 OR:1.34(0.95-1.89)**
Birth weight(g)	2,255±530g	2,121±558g	**<0.001**
Apgar score <7 at 5' 1st and 2nd twin	6 and 19 (1.9%)	5 and 9 (2.6%)	P=0.15 OR:0.70(0.37-1.4)

*Including: Abnormal Doppler, RCIU, Discrepancy>25%, ultrasound or CTG with signs of fetal distress

We found statistically significant differences with respect to fetal malpresentation and signs of fetal distress. This could be explained by the fact that twin pregnancies with fetuses with abnormal Doppler, IUGR or discrepancy >25% were usually scheduled for elective CS before spontaneous labor and at an early gestational age. Elective CS due to fetal malpresentation was normally scheduled at 36-37 weeks in MC-DA twins and 37-38 weeks in DC twins. Naturally, twins from labor CS have a lower mean gestational age at delivery and the newborns a lower birth weight.

Finally, analyzing puerperal complications as we did in our sixth paper **- Puerperal Complications Following Elective Cesarean Sections for Twin Pregnancies,**, we do not find statistically significant differences with respect to mean maternal stay in the hospital, postpartum hemorrhage or scar infection, Table 32.

Table 32 - Puerperal complications

Adapted from: Valdoleiros et al. [192] Maternal morbidity following CS for twins. Cesarean Delivery Meeting. Lisbon 19-20 April 2013 (Poster presentation)

	Elective CS	Labor CS	p-value OR(95%CI)
Mean maternal stay in the hospital(days)	3.7±1.5	3.8±1.6	P=0.7
Postpartum hemorrhage	28(4.2%)	10(3.8%)	P=0.39 OR:1.1(0.54-2.44)
Scar infection	12(1.8%)	8(3%)	P=0.13 OR:0.59(0.24-1.5)

Our low rate of postpartum hemorrhage could be attributed to the protocol of preventive use of 400 mcg misoprostol rectally after any twin delivery in addition to the oxytocin bolus.

However, we must note that both of our studies were limited by several factors

1. Protocols regarding maternal stay in the hospital have changed over time. In the beginning of the 90's women stayed hospitalized 7 days after CS and almost all the cases of scar infection were recorded. A few years later the protocol was changed to 5 days, and since 2004 they only remain hospitalized for 3 days.
2. MAC is a referral center, so the patients come from private doctors, very often from other public hospitals and sometimes even from other cities.
3. Thromboembolism occurring after birth is frequently missing from the records, as this complication is not attributable to the pregnancy or the delivery, and patients are thus referred to other specialties.
4. Even in cases from our area of reference, our reports are dependent on the patients with puerperal complications coming back to our services.
5. We do not have nurse home services to monitor puerperal problems

Because of all these reasons, puerperal morbidity is probably underestimated in our records and long term maternal morbidity is completely unknown.

In conclusion, and according to our experience, CS is a safe procedure both for the fetus and the mother, and should be equated in all situations in which a vaginal twin birth would be risky.

Chapter VI. Conclusion

VI.Conclusion

From the results of my investigation and the trends of current publications of other authors, I may state as conclusions:

1. Elective birth of twins was associated with a significant reduction in the risk of serious adverse outcome for the infants [110,112,113,123,133,179,181,186,195].

2. The optimal time of delivery for women with an otherwise uncomplicated twin gestation varies depending on multiple factors, including chorionicity and amnionicity [196]. Current recommendations suggest that the **optimal time of delivery** for DC twins is 37-38 weeks [195,196,197,198], 36-37 weeks for MC-DA twins [177,178,181,183,253] and 32-34 weeks for MC-MA twins [196,197,199,200,244].

3. The **mode of delivery** recommended for DC and MC-DA twins depends on the presence or not of a previous uterine scar, fetal presentation, gestational age and the provider experience of the obstetrical team [196,197,244].

4. A **vaginal delivery** could be considered in late preterm and term pregnancies [210], for vertex-vertex twins and vertex-non vertex twins where the provider's skills and experience allow it [196,244], and it is safe in MC-DA twins [132,185,186,195, 196,197,199,203, 204]. The most appropriate route of delivery for preterm twins lighter than 1500g remains unclear [210,244], however CS delivery could result in less mortality when birth weight is between 500 and 749g [246].

5. Protocol for induction of labor used in singletons is applicable to twins [185,186,201], and misoprostol is safe for labor induction in twin gestations [129,130,185,186,195,201,202].

6. A **Cesarean section** is recommended in MC-MA, non-vertex presenting twin when the second twin is ≥40% larger than the presenting twin [210], and in women with a uterine scar. However, the French College of Gynaecologists and Obstetricians (CNGOF) believes there is no reason to recommend one type of delivery over another even in a twin pregnancy near term with the first twin in breech presentation, or in women with uterine scars [197,206]. The uterine rupture rate reported in two trials of vaginal delivery for twins after CS varies from 0.8-1.1% [211,212].

7. Taking into account that there is no data showing a clear advantage of a planned CS for twins in terms of short term complications [128,131,133,192,205], patients should receive thorough information about the risks of vaginal and CS deliveries and the **vaginal route** should be performed under epidural analgesia and by an obstetrician with experience in obstetric maneuvers [197].

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